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THE AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

APRIL, 1944

ORIGINAL ARTICLES

"CARDIAC" OR CONGESTIVE CIRRHOSIS

PATHOLOGIC AND CLINICAL ASPECTS

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The purpose of this study was to determine the nature of the fibrosis of the liver in chronic passive hyperemia, its frequency, and its relation to various forms of cardiac disease. A diagnosis of cirrhosis was accepted only when, in addition to fibrosis, there was definite alteration of architectural pattern. In certain instances, the fibrosis and structural alterations were comparatively slight rather than well marked, and focal rather than widespread. Any borderline cases of this sort were not included as cirrhotic livers.

The term cardiac cirrhosis has gained widespread usage. However, congestive cirrhosis is a more accurate designation since it applies directly to the condition in the liver.

Materials and Methods. The cardiac diseases included endocarditis lenta, syphilitic heart disease, cor pulmonale, coronary thrombosis, hypertensive heart disease, chronic constrictive pericarditis, and rheumatic heart disease, divided as to forms into cases of aortic stenosis, of mitral stenosis, and combined valvular lesions. Mitral stenosis was always present in the cases of combined valvular disease together with deformity of either or both the aortic and tricuspid valves. The syphilitic heart disease included aortic insufficiency. The cases of coronary thrombosis showed remote or recent occlusion with myocardial infarction, and in 12 of these cases there was associated hypertension.

A group of 25 cases was selected for each type of cardiac disease except constrictive pericarditis, in which only 8 were available. This gave a total of 208 cases. In every instance the heart disease was the primary clinical lesion and the patient showed congestive failure.

After the number of cirrhotic livers in each type was determined, a survey was made of the 4200 consecutive autopsies from which the various groups were drawn, and the additional cases of cirrhosis included in the study.

Microscopically, sections from both lobes of the liver, stained with hematoxylin and eosin, were examined. Stains for iron-containing pigment, and

for connective tissue by the azan carmine method were made in all cases. In some instances stains were prepared for reticulin.

The livers were studied for thickening and condensation of stroma, degree and distribution of fibrosis, necrosis and regeneration of parenchyma, and distortion of lobular pattern.

Weights of the liver and spleen were recorded, also the presence at autopsy of ascites, jaundice, edema, and obstruction of the portal circulation.

The clinical data for all cases included duration of cardiac failure, number of attacks of decompensation, palpability of the liver and spleen, ascites, jaundice (icterus index level) and blood proteins.

Results. There were 21 livers with cirrhosis among the 208 cases of cardiac disease. These were distributed as follows: 1 each in the groups of cor pulmonale, coronary thrombosis (this patient also had hypertension), and rheumatic heart disease with aortic stenosis; 2 in the group of hypertensive heart disease; 5 in patients with chronic constrictive pericarditis; 4 in cases of rheumatic heart disease with pure mitral stenosis, and 7 in rheumatic cases with combined valve lesions.

Nine additional instances of congestive cirrhosis were found in reviewing the 4200 autopsies covering the study. There were 3 cases in patients with rheumatic heart disease, 2 in patients with hypertension, and 1 each in a case of arteriosclerotic heart disease, combined hypertension and cor pulmonale, and combined rheumatic and congenital heart disease. One case occurred in a 32 year old male with congestive failure of unknown etiology.

The total of 30 cases of congestive cirrhosis was distributed as shown in Table 1.

TABLE 1.—DISTRIBUTION OF 30 CASES OF CONGESTIVE CIRRHOSIS AMONG VARIOUS TYPES OF HEART DISEASE IN 4200 AUTOPSIES

Type of heart disease	Number of cases of congestive cirrhosis
Cor pulmonale	1
Coronary thrombosis	1
Hypertensive heart disease	4
Chronic constrictive pericarditis	5
Rheumatic heart disease:	
Aortic stenosis	1
Mitral stenosis	5
Combined valvular disease	9
Arteriosclerotic heart disease	1
Hypertension and cor pulmonale	1
Rheumatic and congenital heart disease	1
Heart disease of unknown etiology	1
Total	30

The groups in which there was the slightest degree of hepatic fibrosis were endocarditis lenta, coronary arterial disease, and aortic stenosis. The livers generally revealed thickening or condensation of the intralobular stroma. Fibrosis was observed in only a few instances and consisted of small foci in the portal or central zones of the lobules.

Fibrosis of the liver was more prominent in the cases of syphilitic heart disease, cor pulmonale, and hypertensive heart disease, especially the latter. Many livers of the syphilitic group showed condensation

of stroma, accompanied in 5 instances by focal proliferation of fibrous tissue. In cases of cor pulmonale and hypertension, focal hepatic fibrosis of slight or moderate degree was frequent and there was a tendency to anastomosis of fibrous tissue between lobules. The latter was sufficiently widespread to diagnose cirrhosis in 1 case of cor pulmonale and in 2 of hypertension. Moreover, 3 hypertensive cases showed a degree of fibrosis consistent with a diagnosis of slight cirrhosis.

The livers of the patients with rheumatic heart disease were frequently the seat of fibrosis. The increase in connective tissue varied from slight to marked and was focal or moderately diffuse. Four of the 25 patients with pure mitral stenosis and 7 of the 25 with combined valvular disease had congestive cirrhosis. Of the total of 30 cirrhotic livers, 15 occurred in patients with rheumatic heart disease.

The most severe grade of hepatic fibrosis occurred in patients with chronic constrictive pericarditis. Five of the 8 livers from patients with this cardiac lesion were the seat of definite cirrhosis and in 2 others there was slight cirrhosis.

Of the 30 cases 16 were in males and 14 in females. There was 1 colored patient and the rest were white. The range of age distribution was wide (14 to 74 years), but the majority of patients were between 30 and 50 years.

All patients with cirrhosis had congestive heart failure, generally severe and of long duration, *i. e.*, 1 to 14 years. In 10 cases there was continuous cardiac insufficiency, apparently without significant improvement, for a period of 1 to 10 years. In 20 cases there was a history of repeated episodes of decompensation. This was especially true of the rheumatic group in which the number of hospital admissions for decompensation ranged from 3 to 14, usually over a period of years.

TABLE 2.—COMPARISON OF CASES OF CHRONIC PASSIVE HYPEREMIA OF THE LIVER WITH CASES OF CONGESTIVE CIRRHOSIS

Type of heart disease	No. of cases	Weights of liver			Weights of spleen		Ascites*	Jaundice
		1500 gm. or less	1501–2000 gm.	Over 2000 gm.	200 gm. or less	Over		
Endocarditis lenta	25	5	12	8	2	23	8	2
Syphilitic heart disease	25	11	12	2	14	11	11	0
Cor pulmonale	24	16	7	1	18	6	10	0
Coronary thrombosis	24	14	9	1	20	4	4	0
Hypertensive heart disease	23	8	11	4	18	5	10	0
Chronic constrictive pericarditis	3	2	1	0	2	1	1	1
Rheumatic heart disease:								
Mitral stenosis	21	12	10	2	14	10	8	7
Aortic stenosis	24	13	7	1	10	11	9	2
Combined valvular disease	18	10	8	0	9	9	8	5
Total	187	91	77	19	107	80	69	17
Congestive cirrhosis	30	20	7	3	13	17	12	12

* At least 250 cc. of fluid were required for this diagnosis.

Table 2 gives the weights of the liver and spleen, also the presence of ascites and jaundice in the 30 cases of cirrhosis. Similar data are recorded for 187 livers, the seat of chronic passive hyperemia. The latter represent the non-cirrhotic livers in the various etiologic types

of heart disease. The figures show that, in the cirrhotic group, there is a tendency to smaller livers, larger spleens, and more frequent incidence of jaundice. A few large spleens, weighing up to 650 gm., were present in both groups.

Comment. The 5 cirrhotic livers from patients with chronic constrictive pericarditis showed the most extensive fibrosis and distortion of architectural pattern of the entire group. Increase of connective tissue was especially prominent in the portal zones, together with proliferation of bile ducts. All the patients had prolonged hepatic venous stasis due to mechanical obstruction to venous outflow. Cardiac incompetency was more or less continuous for a period of 2 to 10 years. In the 3 cases without cirrhosis, cardiac failure was of shorter duration (4 to 14 months). Six patients died shortly following pericardiectomy and 1 patient died of unrelated cause 21 months after operation. Compared with other forms of heart disease, chronic constrictive pericarditis is infrequent.

Congestive cirrhosis is relatively common in rheumatic heart disease. It is found only in connection with marked valvular deformity. Except for 1 case of pure aortic stenosis, all patients in this group had "button-hole" mitral valves. The latter occurred either alone or in combination with deformity of other valves, especially aortic and tricuspid. In 3 cases there was stenosis and insufficiency of all four valves. The patients in this group with cirrhosis had in common a long history of cardiac incompetency with periods of improvement and failure.

Our survey of 4200 autopsies showed 103 cases of marked rheumatic valvular deformity, in 15 of which congestive cirrhosis was present. Omitting 25 instances of pure aortic stenosis, the 15 cirrhotic livers occurred among 78 rheumatic hearts, an incidence of 19%. Breaking the figures down further showed 5 cirrhotic lesions among 32 patients with pure mitral stenosis (16%) and 8 lesions among 46 patients with combined valvular disease (17%).

There were 30 patients with tricuspid stenosis, 7 of whom (23%) had congestive cirrhosis. Although the incidence of cirrhosis is somewhat higher in cases with tricuspid stenosis, the latter is probably not of significance *per se*, since narrowing of the valve lumen is generally slight. The important consideration is that patients with tricuspid stenosis have had recurrent attacks of rheumatic fever and develop marked deforming rheumatic heart disease, usually polyvalvular, with cardiac failure of long duration.

On a percentage basis, cirrhosis occurs less frequently in hypertensive than in rheumatic heart disease. However, the livers of hypertensive patients often show a definite tendency to fibrosis. The latter is usually slight or moderate, focal rather than diffuse, and prominent in portal location. The last may result in an incorrect diagnosis of early Laennec's cirrhosis.

The cirrhotic lesion is uncommon in cor pulmonale in spite of primary right ventricular failure. Patients with this lesion show progressive dyspnea, often for several years, but frank decompensation is

usually terminal. Also, the pulmonary disease probably accounts in part for the long history of dyspnea.

Congestive cirrhosis is uncommon or rare in patients with pure aortic stenosis, syphilitic aortic regurgitation, coronary thrombosis, or endocarditis lenta. In aortic stenosis or regurgitation, cardiac failure is often abrupt and its duration comparatively brief with few or no intervals of improvement. In some cases of coronary thrombosis in this study, heart failure followed an acute thrombotic occlusion and was of short duration. Other patients had survived episodes of occlusion up to 8 years previously and showed one or more healed infarcts at autopsy. Repeated attacks of decompensation were uncommon. Patients with endocarditis lenta, in whom long-standing heart failure is rare, showed the least severe grade of passive hyperemia of the liver. Death was generally due to the effects of bacteremia and embolism.

Incidence of Congestive Cirrhosis. Among 4200 consecutive autopsies at this institute, there were 164 cases of cirrhosis of the liver (4%). Of the four main types, there were 74 cases of Laennec's cirrhosis, 31 of obstructive biliary type, 30 of congestive cirrhosis, and 15 of toxic cirrhosis. The congestive lesion comprised 18% of the cirrhotic livers and occurred in 0.7% of the total number of autopsies.

These figures are similar to those of Ophüls,[13] who gave an incidence of 0.7% for congestive cirrhosis, *i. e.*, 22 cases among 3000 autopsies, and to those of Boles and Clark[2] who had 33 cases among 4000 autopsies (0.8%). The latter found congestive cirrhosis second in frequency to the Laennec type. In 6548 autopsies reviewed by Garvin,[5] there were 790 adults dead of heart disease and 35 (4.4%) of these had congestive cirrhosis. Out of 75 cases of heart disease with either a prolonged single or multiple episodes of congestive failure, Boland and Willius[1] accepted a diagnosis of cirrhosis in 5 (7%). Menne and Johnston[11] reported 17 cases of congestive cirrhosis among 6500 autopsies but did not include them in the category of true cirrhosis.

Morphology. Grossly, the liver of congestive cirrhosis is firm, retains the usual shape, and is normal or slightly reduced in size. The capsule is thickened, opaque, and slightly uneven or nodular. The color varies from the usual purplish brown to brownish or yellowish red. In our 30 cases the weights ranged from 850 to 2600 gm.; 20 livers weighed 1500 gm. or less, while 7 weighed from 1501 to 2000 gm.

The organ cuts with increased resistance, revealing a nodular cross-section which shows diffuse alteration of the lobular structure. Discrete or confluent gray or yellowish gray nodules from 1 to 5 mm. in diameter, elevated and irregular in outline, are separated by interlacing brownish red retracted zones of varying size and shape. When confluent, the nodules form prominent foci isolated among the hyperemic zones, and appear to be composed of enlarged and distorted liver lobules. Usually no bile staining is present, but in some instances patchy yellow or yellowish green foci are observed, especially in the firm retracted zones. The appearance sometimes resembles that of the so-called nutmeg liver, which may represent a stage in the development of cirrhosis.

Microscopically, the central zones show slight to marked hyperemia. Sometimes there is accumulation of blood which obliterates the architectural pattern. The changes in the liver cells range from slight atrophy to degeneration or necrosis. The necrotic zones vary in size and shape, and often show an asymmetric distribution around the central veins. They may be situated primarily to one side of these veins, and extend to the periphery of the lobule. Anastomosis of hyperemic foci in adjacent lobules produces an irregular pattern in which portal spaces are isolated or joined to central zones.

The stroma of the central zones is thickened and prominent. There is an increase of reticulin and deposit of intercellular collagen to form compact fibrous bands. Fibrosis also occurs in the portal regions, accompanied by proliferation of bile ducts and infiltration of lymphocytes. These changes are sometimes pronounced. Both the portal zones and the intralobular stroma serve as a source of connective tissue. Although generally observed in both central and portal regions, the fibrosis may predominate in either one. The connective tissue is usually compact and relatively acellular, but active growth is indicated by the presence of young fibroblasts in both regions. In well-developed cases, bands of fibrous tissue extend within the lobules from the central to the peripheral zones and also connect central or portal zones in adjacent lobules.

The so-called regenerative foci, which correspond to the elevated gray or yellowish gray nodules in the gross, are composed of parts of adjacent lobules or whole lobules, especially the peripheral zones. There are groups of large liver cells, irregular in outline and containing abundant granular cytoplasm. The cord arrangement of the cells is usually preserved. Only slight hyperemia and fibrosis occur in such foci. Cellular activity is indicated by the presence of single or double nuclei ranging from small and hyperchromatic to large and vesicular. However, since actual cell division is generally not demonstrable, the degree of parenchymal regeneration is uncertain. The changes may be largely functional and due to hypertrophy of less injured cells.

The usual lobular pattern is altered. Portal spaces undergo eccentric change in position and several of them are often in close proximity. Central veins are displaced and lose their normal relation to the lobules. The latter are reduced or increased in size and in many situations their boundaries cannot be defined. Fusion of hyperemic zones and of connective tissue bands produces partial or complete isolation of pseudolobular groups of liver cells which lack connection with a central vein.

Hemosiderosis, as shown by special stains for iron-containing pigment, is infrequent. No hemosiderin was found in 18 of the 30 cases in this study. The amount was minimal or slight in 7 cases and moderate in 5 cases. When present, the pigment was generally situated in both parenchymal and Kupffer cells in or at the periphery of the hyperemic zones. These findings favor the view that venous stasis of the central regions is usually not accompanied by significant hemorrhage. Some extravasation of erythrocytes occurs, but the cells may apparently remain intact for a considerable period.

Variation in morphology is characteristic of congestive cirrhosis. Necrosis of parenchyma varies in degree in the brownish red retracted zones. Fibrosis is prominent in the latter regions and slight or absent in the regenerative foci. The connective tissue varies in amount and location. Portal fibrosis, mixed portal and central fibrosis, and pure central fibrosis may be intermingled in nearby situations.

The gross and microscopic appearance of the liver is essentially similar for the various etiologic types of heart disease. However, in this study a tendency was noted for greater prominence of portal fibrosis in lesions accompanying constrictive pericarditis and hypertension than in those associated with rheumatic heart disease.

Pathogenesis. Degeneration and necrosis of hepatic parenchyma in chronic passive hyperemia occur mainly in the central zones. Although the lesion is sometimes referred to as pressure atrophy and necrosis, direct compression of cells by dilated sinusoids is not significant.[4,9] The changes are probably due to the prolonged anoxia which accompanies venous stasis and is most severe in the central regions.[4,8,9,12] The primary injurious factor is the passive hyperemia itself.[1] That infectious or other injurious agents[10,15] unrelated to venous stasis commonly play an additional rôle is not proven, even though impairment of circulation may predispose the liver to such action.[3] No such agents could be established in this study. Marked hepatic necrosis has been produced experimentally under conditions which apparently eliminate toxic or infectious factors.[4,16]

Degeneration and necrosis of parenchyma are followed by thickening and condensation of the stroma and finally by proliferation of fibrous connective tissue. The latter may represent the reaction of the stroma to anoxemia or possibly to injurious products released by passive hyperemia. Katzin *et al.*[7] found an increase in incidence and severity of hepatic fibrosis with increasing duration of congestive heart failure. Fibrosis frequently accompanies atrophy of parenchyma in any organ, and Karsner[6] points out that this is true of the cellular atrophy caused by prolonged passive hyperemia. As cells are injured and destroyed, the products of disintegration stimulate a low grade of inflammation that results in fibrosis. Moreover, the continued presence of edema may incite fibrosis.

In the experimental lesions produced in dogs by compression of the inferior vena cava, Zimmerman and Hillsman[16] found early necrosis of liver cells, Kupffer cells, and perilobular connective tissue. There was active proliferation of fibrous tissue. However, the fibrosis was purely central and failed to increase in extent after 85 days. The authors observe that the rapid course and progressive nature of the lesion in these animals differ from patients with congestive heart failure who often show periods of arrest or improvement.

Some doubt exists as to whether congestive cirrhosis is a progressive lesion in the sense of persistent action of the injurious agent, or continuous progress of the lesion morphologically. Those cases in which the lesion appears to be progressive clinically, have usually been attributed to repeated episodes of congestive heart failure. Boland

and Willius[1] even doubt that fibrosis can occur in the liver except in periods of recovery from decompensation.

In our group of 30 patients, 20 gave a history of repeated attacks of failure, while 10 showed progressive failure without apparent remission. Nevertheless the latter may have had intervals of improvement with relief of hepatic venous stasis. It appears likely that recurrent episodes of decompensation promote the development of congestive cirrhosis.[1] However, this does not exclude production of the lesion as the result of severe, persistent venous stasis.

In Zimmerman and Hillsman's animals, the lesions of the liver, including the fibrosis, were steadily progressive for 85 days. Bolton's work suggests that failure to extend beyond this period may be due to establishment of collateral anastomoses.[4] Persistent mechanical interference with venous outflow from the liver, induced by constricting the inferior vena cava, is comparable in man to chronic constrictive pericarditis. The latter produces continuous and severe venous stasis of the liver. The development of congestive cirrhosis in such cases, as in 5 of the 8 patients in this study with constrictive pericarditis, is highly suggestive of a progressive process.

Comparison With Laennec's Cirrhosis. Congestive cirrhosis does not develop the extreme structural distortion and the extensive fibrosis and regeneration observed in the Laennec type. Moreover, the distribution of the lesion through the organ lacks the uniformity of the Laennec type. In the latter the causative agents produce severe, diffuse injury to parenchyma and mesenchymal framework. Congestive cirrhosis results from prolonged venous stasis and the injurious effect on the liver is less intense. Lack of uniform distribution through the organ is probably due to difference in degree of stasis in the radicles of the hepatic vein.

The morphologic distinction between well-developed Laennec's and congestive cirrhosis is simple. Differentiation of the early stage of Laennec's cirrhosis from the congestive lesion may be difficult. Microscopically, the portal fibrosis occurring in each form is indistinguishable. Central fibrosis is confined to patients with congestive heart failure.[7] Even when the fibrosis is chiefly portal in location, the congestive form usually shows central hyperemia with atrophy or necrosis of parenchyma. Moreover, in congestive cirrhosis the nodules of liver parenchyma are irregular in shape and show anastomosis, while those of Laennec's cirrhosis tend to be round, circumscribed, and isolated. Should early Laennec's cirrhosis be complicated by congestive heart failure, distinction may be impossible.

Some observers doubt that the term cirrhosis can be properly applied to livers the seat of chronic passive hyperemia. The main objections are that the fibrosis represents chiefly condensation of stroma and that the architecture is altered in a false rather than real sense, with limitation of nodularity to the region of sublobular veins. Lambert and Allison[8] held that chronic passive hyperemia does not produce cirrhosis of the usual portal or nodular type.

In this study, proliferation of connective tissue and distortion of

architectural pattern were the diagnostic criteria. Fibrosis was moderately diffuse, was active as indicated by the presence of fibroblasts, led to the formation of anastomosing collagenous bands, and was distinctive from mere condensation of stroma. The term was not applied to livers with focal fibrosis, nor to lesions principally subcapsular in position or confined to the lower portions of the two main lobes. Alteration of structural pattern was indicated by displacement of veins, isolation of nodular groups of liver cells, and frequent loss of identity of original lobular units.

The frequency of congestive cirrhosis depends on the criteria used for diagnosis and their interpretation. Accordingly, the lesion has been held to be non-existent,[8,11] rare,[1] or moderately frequent.[6] A liberal view of the concept of cirrhosis would permit inclusion of a congestive form of the disease. The term congestive cirrhosis is useful from a morphologic standpoint. There is, however, the reservation that the lesion is much less severe and less uniformly distributed through the organ than is Laennec's cirrhosis.

Clinical Diagnosis. A clinical diagnosis of congestive cirrhosis was made in 3 of the 30 cases in our study. This diagnosis is generally inaccurate because congestive cirrhosis as a group shows no distinctive features in comparison with organs the seat of advanced passive hyperemia. Apparent increase in size of the liver, ascites, jaundice, and palpable spleen are not adequate criteria; they are the result of decompensation and occur in both groups. The changes in stroma and vascular bed of the liver in congestive cirrhosis are not sufficient to produce portal obstruction. Blood protein levels are similar in the two groups and are generally reduced—a common finding in cardiac decompensation.[14] No investigation of liver function was made in our cases, but the studies of Boland and Willius[1] indicate that no significant differences are encountered in congestive cirrhotic and non-cirrhotic livers. Functional impairment appears to be an index of parenchymal atrophy and necrosis rather than cirrhosis. Marked decrease in function is rare.

Perhaps the best clues as to the presence of congestive cirrhosis clinically are obtained from the patient's history and the causative type of heart disease. The development of cirrhosis is favored by long-standing failure, especially with numerous episodes of decompensation. The lesion frequently accompanies chronic constrictive pericarditis and is relatively common in rheumatic heart disease. Garvin found that rheumatic and hypertensive heart disease were the types most commonly associated with cirrhosis.[5] His study included no cases of constrictive pericarditis.

Summary and Conclusions. Livers the seat of prolonged and advanced passive hyperemia, due to heart failure, sometimes show diffuse fibrosis and alteration of architectural pattern. These may properly be designated congestive cirrhosis. However, the degree of fibrosis and distortion of architectural pattern are considerably less than in well-developed Laennec's cirrhosis.

The main etiologic factor is prolonged and severe hepatic venous

stasis. Repeated episodes of decompensation favor the development of the lesion.

The most severe degree of fibrosis and architectural change occurred in patients with chronic constrictive pericarditis. The continual venous stasis in such cases suggests that the cirrhosis develops as a progressive process.

Congestive cirrhosis is relatively common in patients with rheumatic heart disease, both in those with mitral stenosis or with combined valvular lesions. It is less frequent in hypertensive patients and is uncommon or rare in other etiologic forms of heart disease.

The clinical aspects of congestive cirrhosis do not provide adequate data for antemortem diagnosis.

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ANNULAR PANCREAS

A Tabulation of the Recent Literature and Report of a Case

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The anomalous condition known as annular pancreas is reputedly rare, there having been less than 50 cases reported up to 1943. McNaught[5] was able to find 40 cases in the period from 1918 to 1932 and reported them collectively in 1933. It is apparent that in the intervening decade this condition made more frequent appearances in the literature. In 1935 McNaught[6] reported 3 additional cases which he had found in the literature and added 1 more of his own. More recently 2 others have appeared, one by Cunningham,[4] the other by Truelsen.[10] The pertinent facts of these additional cases and of the

case reported below are listed in Table 1. This table, together with that of McNaught,[5] completes the tabulation of the entire series of 47 cases.

The increasing frequency of case reports on annular pancreas suggests that the true incidence is probably higher than the available figures indicate. This contention is supported by the fact that within 14 years 3 cases of this anomaly have been found in the autopsy material at Receiving Hospital. From the time that Brines[1,2] encountered the 1st case until the 3rd case was found there were 7095 autopsies. This makes an incidence of 0.0412%, approximately 1 in every 2500 autopsies.

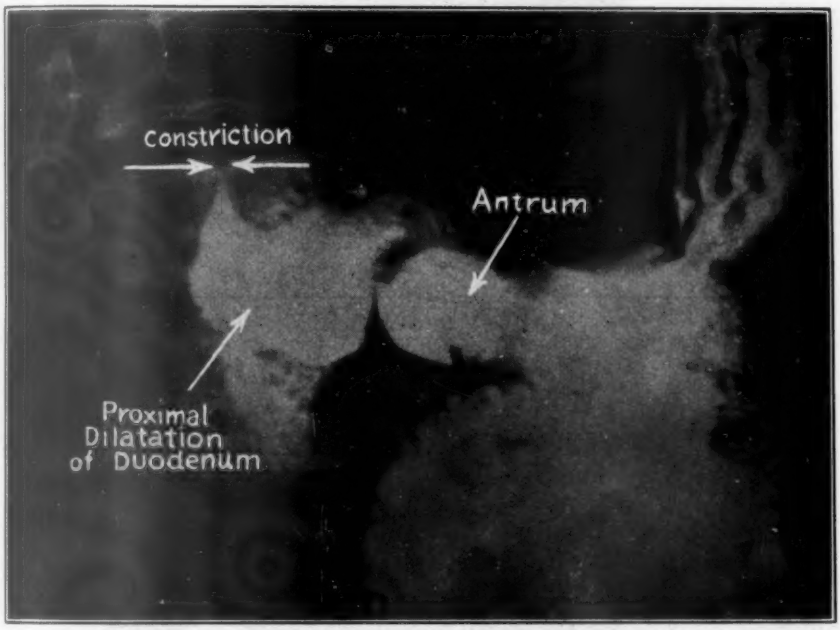

FIG. 1.—The roentgenographic appearance of the duodenum constricted by annular pancreas. The dilated proximal portion includes the bulb and proximal half of the second portion of the duodenum.

The 2 early cases in the series at Receiving Hospital were complicated by gastro-intestinal lesions, the first by acute hemorrhagic pancreatitis and the second by peptic ulcer. Further details are not included.

Case Abstract. The last of the series was a white male, age 62, who had previously been under observation for depressive psychosis. He was admitted for the last time on October 27, 1942, because of his mental state. The history from the relatives revealed that he had been vomiting several times daily for the past 6 months. Physical examination showed emaciation, a normal chest and abdomen, external hemorrhoids, and well healed amputations of the great toes. By Roentgen ray an abnormality of the duodenum was demonstrated which was interpreted as a diverticulum (Fig. 1). The patient was put on a medical régime in an effort to improve his condition so that an explor-

atory laparotomy could be done. He failed to respond and died on December 4, 1942.

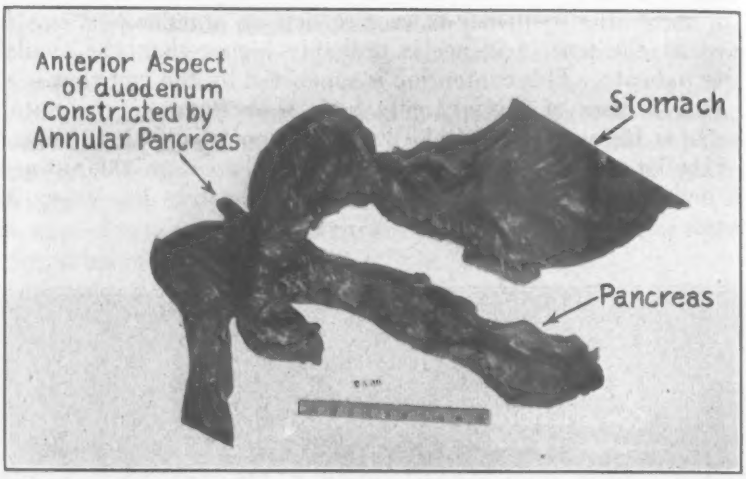

FIG. 2.—The gross specimen showing the dilatation of the duodenum above and below the annular pancreas.

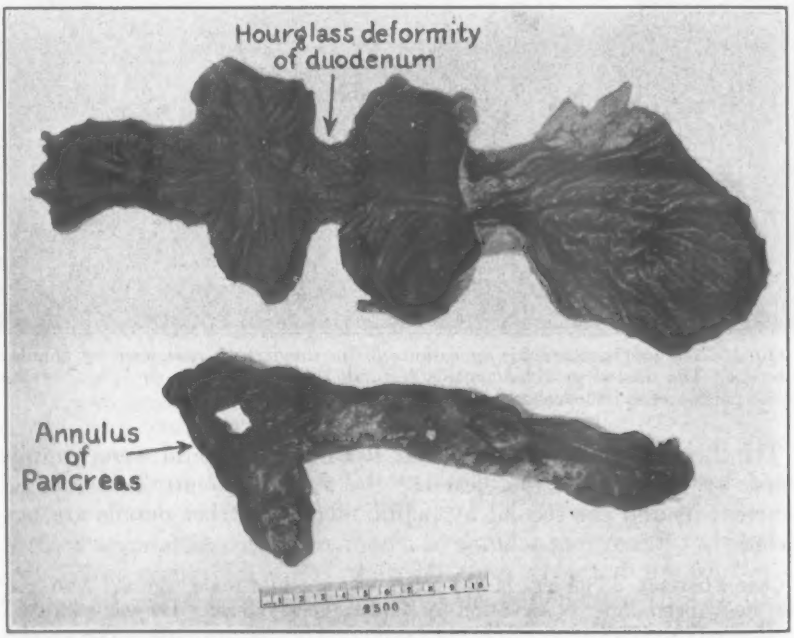

FIG. 3.—The dissected specimen showing the complete ring of pancreatic tissue.

AUTOPSY. An annular pancreas was found, associated with an "hour-glass" deformity of the duodenum and dilatation of the stomach (Fig. 2). In addition, there was an abnormal convolutional pattern in the cerebral cortex, enlarge-

ment of the ventricular spaces, small cavity formation in the globus pallidus, and chromophobe adenoma of the pituitary.*

The ring of pancreatic tissue was complete (Fig. 3). However, on the posterior aspect of the ring near the head of the pancreas the tissue was attenuated, and loose, fibrous tissue composed part of the diameter of the ring at this level. Injection of the duct system in a manner similar to that suggested by McNaught[6] resulted in a failure to demonstrate any connection between the main pancreatic duct and that which, as proven by microscopic section, was present in the annular portion of the pancreas (Fig. 4).

FIG. 4.—The injected pancreas. The main duct system is completely injected. The duct of the annular portion remains uninjected and is apparently entirely separate.

This finding is in accordance with the experience of Cunningham,[4] who in his specimen was able to inject the annular duct system separately. Unfortunately we were unable to accomplish separate injection because of our inability to cannulate the extremely small duct in the annulus of the specimen. However, Schlesinger[8] demonstrated that his injection mass would penetrate any vessel with a caliber

* The examination of the brain was done by Dr. Gabriel Steiner, Chief of the Division of Neuropathology, Wayne University College of Medicine.

greater than 40 microns. Having used the same injection mass and basing our opinion on his work, we feel that the caliber of the annular duct system was sufficient to allow injection by way of the main duct had there been a connection between the duct systems of the main and annular portions. We are therefore in agreement with one theory proposed by Tieken,[9] that annular pancreas is an abnormal development of the ventral pancreatic anlage rather than a localized hypertrophy of a normally formed pancreas.

TABLE 1.—ANALYSIS OF CASES REPORTED SINCE MCNAUGHT'S LIST (1933)

	Age	Sex	Signs and symptoms	Duodenum			Duct in ring	Operation	Associated congenital abnormality
				In volved portion	Con-stric-tion	Dilata-tion			
Cartellieri[3] 1927	9 mo. fetus	M	0	Second	+	+	Not demon-strated	0	Double hiatus of the dia-phragm with visceral dis-placement
Zeck[11] 1931	27	F	Pain in right hy-pochondrium, fulness, tenderness	Second	+	+	Not demon-strated	Incision and transverse suture	0
Reitano[7] 1932	5 mo.	M	Icterus, acholic feces	Third*	+	None†	Not demon-strated	0	Malformation abdominal viscera
McNaught[6] 1935	70	M	None related to pancreas	Second	0	0	Opened into main duct	0	Horseshoe kidney
Cunningham[4] 1940	65	M	0	Second	0	0	Duct separate; opened into common bile duct	0	0
Truelsen[10] 1940	35	M	Epigastric pain, fulness, vomit-ing	Third	+	+	Not demon-strated	Duodenor-rhaphy and gastro-en-terostomy	0
Stofer	62	M	Vomiting	Second	+	+	Separate	0	Cerebral mal-formation

* Not complete.
† Markedly thickened wall.

That other congenital malformations are frequently associated with annular pancreas is well known. In the complete series this association occurs in 12 of the 47 cases (25.5%). Most of these abnormalities are in the gastro-intestinal tract. This is the first case in which the associated abnormality is in the central nervous system.

The roentgenologist was of the opinion that a diverticulum or pseudodiverticulum was present. The diagnosis of diverticulum of the duodenum was offered also in the cases of Zeck[11] and Truelsen.[10] A consistent error of this kind suggests that there might well be cases of annular pancreas in which an erroneous diagnosis of duodenal divertic-

ulum has been made. Greater consideration of the possibility of annular pancreas is justified by this experience.

Summary. The 47th case of annular pancreas is reported, and the incidence in a large series of autopsies is established. Features of the case relative to pathogenesis, associated anomalies, and the clinical diagnosis are briefly discussed.

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THE ELECTROCARDIOGRAM AND THE "TWO-STEP" EXERCISE

A Test of Cardiac Function and Coronary Insufficiency*†

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In many cases of coronary artery disease with angina pectoris the physical examination, the size of the heart and cardiac pulsations, as seen in the Roentgen ray film and fluoroscopically, and the electrocardiogram are normal. There is thus no objective evidence to confirm the diagnosis of coronary sclerosis. In valvular disease patients often complain of symptoms such as dyspnea and pain although the physical examination reveals no evidence of heart failure. In both of these types of cases a functional test, *i. e.*, one that obtains the response of the heart to effort, may be of great value both in diagnosis and the evaluation of functional capacity. Beginning in 1925 one of us developed a test utilizing the response of the blood pressure and pulse rate to a standard "two-step"[9,16] exercise. This measurement of vasomotor response was found to be a practical indication of circulatory fitness. Later the ECG findings following this standard "two-step" exer-

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† Approved for publication by the Division of Publications, Bureau of Medicine and Surgery, U. S. Navy. The assertions herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Naval service at large.

cise were used to reveal the state of the coronary circulation.[10,12,13,14,15] If coronary insufficiency existed, characteristic changes occurred in the ECG. No changes appeared in the presence of adequate coronary circulation.

We are reporting results which for the first time definitely show that the abnormal changes in the ECG following the (Master) "two-step" exercise are due to the lack of oxygen supply to the heart muscle, *i. e.*, coronary insufficiency. Whenever ECG changes appeared after the "two-step" (*e. g.*, RST depressions or T-wave inversions) they were reproduced exactly in the same subject by his breathing a low oxygen concentration, specifically 10% oxygen. When no ECG abnormalities appeared after the "two-step" none appeared on breathing 10% oxygen.

FIG. 1.—The set-up with standard "2-steps" each 9 inches high, an ECG machine, Adirondack chair with wide arms, technician or physician with stop watch in hand, person to be tested with electrodes strapped on and blood pressure cuff and gauge bound around arm.

Procedure of the "Electrocardiogram and Two-step." The electrodes are attached to the patient and the blood pressure cuff placed on his arm (Fig. 1). He is then weighed. He sits down in an Adirondack chair and makes himself comfortable. His name and age are written down and the number of trips he is to make is obtained from the table (Table 1). For example, H.A.K., a man of 55, weighing 164 pounds calls for 19 trips. The electrocardiogram is recorded. Then the blood pressure and pulse rate are taken alternately until they are stabilized, that is, until the last 2 blood pressures and the last 2 pulses

do not differ more than 2 points. (The pulse is taken for 15 seconds and multiplied by 4.) The resting figures are obtained usually in but a few minutes. The technician or physician then gives an actual demonstration by climbing over the steps 2 or 3 times. The examinee at a given signal walks up one side of the steps and down the other, always turning to the same wall or side of the room before each ascent. The candidate makes a climb only when he receives the count and the required number of ascents is completed in 1½ minutes. If the candidate climbs too slowly the counting is made more

TABLE 1.—NUMBER OF TRIPS TO BE PERFORMED IN THE "TWO-STEP" TEST, ARRANGED ACCORDING TO SEX, AGE AND WEIGHT

Weight (lbs.)	Age (yrs.) 5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69
						Males							
40– 49	35	36											
50– 59	33	35	32										
60– 69	31	33	31										
70– 79	28	32	30										
80– 89	26	30	29	29	29	28	27	27	26	25	25	24	23
90– 99	24	29	28	28	28	27	27	26	25	25	24	23	22
100–109	22	27	27	28	28	27	26	25	25	24	23	22	22
110–119	20	26	26	27	27	26	25	25	24	23	23	22	21
120–129	18	24	25	26	27	26	25	24	23	23	22	21	20
130–139	16	23	24	25	26	25	24	23	23	22	21	20	20
140–149		21	23	24	25	24	24	23	22	21	20	20	19
150–159		20	22	24	25	24	23	22	21	20	20	19	18
160–169		18	21	23	24	23	22	22	21	20	19	18	18
170–179			20	22	23	23	22	21	20	19	18	18	17
180–189			19	21	23	22	21	20	19	19	18	17	16
190–199			18	20	22	21	21	20	19	18	17	16	15
200–209				19	21	21	20	19	18	17	16	16	15
210–219				18	21	20	19	18	17	17	16	15	14
220–229				17	20	20	19	18	17	16	15	14	13
						Females							
40– 49	35	35	33										
50– 59	33	33	32										
60– 69	31	32	30										
70– 79	28	30	29										
80– 89	26	28	28	28	28	27	26	24	23	22	21	21	20
90– 99	24	27	26	27	26	25	24	23	22	22	21	20	19
100–109	22	25	25	26	26	25	24	23	22	21	20	19	18
110–119	20	23	23	25	25	24	23	22	21	20	19	18	18
120–129	18	22	22	24	24	23	22	21	20	19	19	18	17
130–139	16	20	20	23	23	22	21	20	19	19	18	17	16
140–149		18	19	22	22	21	20	19	19	18	17	16	16
150–159		17	17	21	20	20	19	19	18	17	16	16	15
160–169		15	16	20	19	19	18	18	17	16	16	15	14
170–179		13	14	19	18	18	17	17	16	16	15	14	13
180–189			13	18	17	17	17	16	16	15	14	14	13
190–199			12	17	16	16	16	15	15	14	13	13	12
200–209				16	15	15	15	14	14	13	13	12	11
210–219				15	14	14	14	13	13	13	12	11	11
220–229				14	13	13	13	13	12	12	11	11	10

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rapid and if the climbing is too fast the counting is made more deliberate. A stop watch or an electric clock with a large second hand is used. At cessation of the exercise the candidate sits down and the 4 leads of the ECG are recorded immediately. At about 1½ to 1¾ minutes later the blood pressure is taken. One should try to finish this reading just about 2 minutes after the completion of the exercise. The ECG is now repeated and the 2 minute pulse rate obtained from this tracing or by radial pulse count. The ECG is repeated at 2 minute intervals until 10 minutes after cessation of exercise. Both the blood pressure and pulse rate 2 minutes after exercise should be within 10 points

of resting levels. Anything above 10 points in the blood pressure and pulse rate is considered abnormal. The following is an illustration:

H.A.K.: Coronary heart disease, age 55, weight 164 pounds; required number of trips 19.

	Blood pressure	Pulse
	114/82	86
	110/80	82
Resting figures	108/80	82
Two minutes after exercise	132/80	94

Conclusion: Lag in return both of systolic blood pressure and pulse rate following "two-step" exercise.

The number of climbs on the steps which the patient performs is obtained from previously prepared tables for normals based on age, sex and weight (Table 1). The tables[8,15] are the results of more than 2000 tests performed at Cornell University Medical College, 1925–29, on normal persons of all ages and both sexes. They were constructed on the basis that the blood pressure and pulse rate should return to the resting levels 2 minutes after cessation of exercise. The 9 inch size of steps, the two together adding up to 1½ feet in height, and the 1½ minute duration of exercise were both chosen after careful and deliberate experimentation and their value confirmed by years of experience. The response of the blood pressure and pulse rate and the ECG are combined in one procedure.

The examinee turns to the same wall or same side of the room, actually a change in direction at each turn, to prevent giddiness which would result in artificial changes in blood pressure and pulse rate. Placing the steps near or against a wall gives a patient a sense of security. In fact, the examiner, further to reassure such a person, can support him by holding his arm and guiding him over the steps provided he exerts no vertical lift.

A large electric clock with a large sweeping second hand may be preferable to a stop watch as it is seen clearly by all. One technician suffices for the test but, if it is desired, one technician or physician records the blood pressure and the pulse and another technician takes the ECG. In this case the one large electric clock is seen clearly by both workers. If the clock is used instead of the stop watch it is practical to start the exercise on a ½ minute mark so that the exercise of 1½ minutes will be completed when the second hand has made a complete revolution, *i. e.*, reached the 12 o'clock hour. If a stop watch is used this is not necessary for at the completion of the exercise the mechanism can be started anew.

Frequently the ECG changes occur only immediately after exercise and so it is important to be able to obtain the 4 leads quickly. We have taken all 4 leads in as short a period of time as 15 to 30 seconds.* Enough heart beats should be registered to have at least 2 or 3 on the same horizontal line as otherwise artificial changes in the RST level occur. At the present time we repeat the ECG at 4 and 10 minute intervals after cessation of exercise, since occasionally a change becomes apparent only late.

Using the PR interval of the ECG as the control level, a depression of the RST segment over 0.5 mm. in any lead is a positive result and does not occur in healthy persons. In other words, the level of the string just following the QRS complex is compared with that immediately preceding this complex.[13] A change from an upright T wave to an isoelectric (flat) or inverted T wave is also an abnormal response; so, too, is a change in the other direction, *i. e.*, a negative T wave to a

* The new "instomatic" type of small portable ECG of the Sanborn Instrument Company has been found to be particularly useful since a change from one lead to another can be made instantly without the necessity of waiting for the light beam to come to rest.

positive. Occasionally premature beats or some more significant arrhythmia, widening of the QRS, large Q waves, prolongation of the PR interval or heart block may appear. All these are concluded to be an abnormal response to the test. As will be seen later, a control ECG with RST depressions and T-wave inversions indicates coronary insufficiency to begin with and hence the exercise test is unnecessary. The combination of the blood pressure and pulse response and the ECG in one procedure saves time as both tests are performed simultaneously. The criteria of abnormality are conservative and have been worked out after experience in many normals.[13]

To obtain evidence that the ECG changes after the "two-step" were caused by anoxemia of the heart muscle, the 10% oxygen anoxemia test was made on every normal control and patient who performed the "electrocardiogram and two-step." Anoxemia, that is, the breathing of oxygen below atmospheric content, as a test for heart function has been suggested for years but Levy and his co-workers[6] first worked out a definite technique.* After the mask was adjusted and made comfortable the patient breathed through it for a few minutes in order to become accustomed to it. Then a control ECG was taken before breathing 10% oxygen. The ECG was repeated every 5 minutes while breathing the mixture of low oxygen for a total duration of 20 minutes unless circulatory collapse, sudden significant fall of blood pressure, syncope, etc., occurred.

Material. The subjects were 84 Navy personnel between the ages of 17 and 66 (Tables 2 and 3). There were candidates for the Navy and patients with coronary heart disease, hypertension, valvular heart disease, effort syndrome, and a miscellaneous group, *i. e.*, chest deformities, congenital heart disease, etc. Thirty-three healthy men served as normal controls (Table 2). The work was done at the National Naval Medical Center, Bethesda, Md.

Results. NORMALS. There were no positive ECG changes following the "two-step" in the 33 normal individuals (Fig. 2). In other words, there were no flattening or inversion of a normal T wave (or the converse) and no depression of the RST segment relative to the PR level of more than 0.5 mm. One youngster, U.L.S. (Case 20), whom we had been using as a normal control for certain experiments, showed depressed RST but this was explained when a Roentgen ray film disclosed that he was an unsuspected case of virus pneumonia. On recovery his "electrocardiogram after the two-step" became normal. A severe upper respiratory infection, gastro-enteritis (Case 22), and occasionally lack of rest and sleep (Case 18), produced changes. The 10% oxygen test caused similar changes. This test is much more severe than the "two-step." For example, it produced almost immediate peripheral vascular collapse in the unrecognized case of virus pneumonia whereas the "two-step" had only tired the boy moderately.

* Ten per cent oxygen was obtained from either the Experimental Diving Unit, Navy Yard, Washington, D. C., or the Ohio Chemical and Manufacturing Company, Cleveland, Ohio. A simple rubber face mask covering nose and mouth was used with 2 pin flutter valves, 1 for inhalation of the 10% oxygen and the other for expiration of carbon dioxide. In other words, there was no rebreathing. Both valves were sensitive and offered negligible resistance to the passage of air.

TABLE 2.—"ELECTROCARDIOGRAM AFTER 2-STEP" AND 10% OXYGEN TEST IN NORMAL CONTROLS

No.	Name	Age	Electrocardiogram: Before test	Changes: 2-Step	Changes: 10% oxygen	Remarks
1	D.M.B	28	Neg.	None	None	
2	R.A.B.	20	"	"	"	
3	F.C.	19	"	"	"	
4	A.S.F.	27	"	"	"	
5	D.K.	18½	"	"	"	
6	Z.L.	26	"	"	"	
7	A.M.A	46½	"	"	"	
8	R.P.M.	20	"	"	"	
9	S.N.	26	"	"	"	
10	S.R.	26	"	"	"	
11	J.S.	37	"	"	"	
12	J.M.S.	27	"	"	"	
13	J.W.T.	25	"	"	"	
14	R.W.L.	23	"	"	"	
15	R.C.W.	25	"	"	"	
16	W.C.B.	20	"	"	"	
17	H.F.H.	23	"	"	"	
18	M.R.L.	26	"	"	RST 1-2-3	O_2 test performed when man sleepless and fatigued
			"	"	None	
19	J.R.Mc	34	"	"	"	
20	U.L.S.	20	"	T 2-3	T 2-3	Pneumonia
			"	None	None	Recovered
21	W.O.P.	26	"	"	"	
22	J.B.W.	20	"	"	"	
			"	T 2	"	Gastro-enteritis
23	M.S.A.	21	"	None	"	
24	H.C.	19	"	"	"	
25	C.C.	17	"	"	"	
26	A.V.E.	19	"	"	T 2; T 3	
27	G.L.G.	19	"	"	None	
28	A.P.H.	20	"	"	"	
29	G.W.L.	28	"	"	"	
30	M.E.Mc.	17	"	"	"	
31	E.G.R.	17	"	"	"	
32	H.T.	18	"	"	"	O_2 stopped at 10 min. apprehensive
33	E.A.T.	21	"	"	"	

TABLE 3.—"ELECTROCARDIOGRAM AFTER 2-STEP" AND 10% OXYGEN TEST IN VARIOUS HEART DISEASES

Coronary Heart Disease

34	W.G.B.	66	Ventr. prem. beats; T 2 inverted	T 2, T 3; RST 2	T 2, T 3, RST 1-T 4	
35	J.A.C.	59	Neg.	T 2, T 3	T 2, T 3	
36	D.M.C.	49	T 1-2-3-4 inverted	T 2-3-4	T 1	
37	E.D.C.	44	Neg.	None	None	
38	D.A.D.	35	140/min. RST 1-2-3, depressed, T 1-2-3 semi-inv.	"	"	
39	A.J.D.	60	QRS 0.11, Q 1-4, T 1-4 inv.	T 1-2-4	T 1-4	
40	G.A.G.	46	Neg.	None	None	
41	J.H.G.	63	QRS low, Q 4, T 1 inv.	T 1	T 1	
42	R.S.H.	60	PR = 0.28	None	Nodal rhythm	O_2 stopped at 6 min.; collapsed
43	F.O.H.	44	Neg.	"	None	O_2 stopped at 5 min.; nausea, dyspnea
44	H.A.K.	55	"	RST 1-2-3-4, T 1-2-3-4	RST 1-2-3-4, T 1-2-3-4	
45	R.S.K.	59	Neg., P 2-3 inv.	P 2-3, Q 4	P 2-3	
46	P.S.L.	57	T 1 flat	T 1-2	T 1	
47	H.P.Mc.	45	Q 3, T 2-3 inv.	T 2	T 2	
48	O.P.	44	QRS notched, Q 2-3	None	None	
49	W.H.S.	48	Neg.	T 1-2	None	O_2 stopped at 17 min.; collapsed

TABLE 3.—(*Continued*)

No.	Name	Age	Electrocardiogram: Before test	Changes: 2-Step	Changes: 10% oxygen	Remarks
50	L.P.S.	51	QRS 0.12	RST 1, T 1	RST 1, T 1	
51	Mrs. C.P.S.	63	Neg.	RST 1–2–4, T 1–2–4	RST 1–2–4, T 1–2–4	
52	H.S.	63	QRS 0.11, Q 2–3, T 2–3 inv.	None	None	O_2 stopped at 15 min.; collapsed
53	J.E.T.	44	T 1–2 inv., Q 3	T 1	T 1	
			Valvular Heart Disease			
54	H.L.A.	20	Neg	None	None	
55	V.L.A	20	P 2–3 notched, QRS high, Q 2–3, RST 2–3, T 2–3 inv.	"	"	O_2 stopped at 11 min.; mild shock
56	L.A.C.	25	T 2–3 inv.	T 2	T 2	
57	W.P.F.	23	T 2 flat	T 2–3	T 2–3	
58	H.M.G.	27	QRS 0.12, right axis deviation	RST 2, T 2	T 2	
59	H.T.H.	37	Neg.	RST 2–3	RST 2–3	
60	D.C.L.	23	"	None	None	O_2 stopped at 15 min.; peripheral failure
61	H.F.A.L.	39	Neg. P 2 notched	"	"	
62	Mrs. C.L.	22	105 per min., T 2 flat, T 2 inv.	T 2	T 2	
63	M.E.Mc.	24	Neg.	None	None	
64	Mrs. C.S.	25	P 2–3, RST 2–3, T 2–3 semi-inv., T 4 inv.	RST 2–3	T 1–2–3–4	O_2 stopped at 15 min.; cyanosis
65	Mrs. L.T.S.	35	Neg. 120 per min.	None	None	
66	E.M.T.	25	Neg.	RST 2–3, T 1–2–3–4	RST 1–2, T 1–2–3–4	
			Hypertension			
67	L.A.	52	Neg., P 2 notched	None	None	O_2 stopped at 16 min.; B.P. 144/94
68	M.W.B.	42	Q 3	"	"	O_2 stopped at 7 min.; asleep, B.P. 160/120
69	J.H.S.D.	64	RST 1–2	"	"	B.P. 160/84
70	H.T.D.	52½	Neg.	"	"	B.P. 170/120
71	J.R.E.	41	RST 2, T 1 inv.	"	"	B.P. 176/116
72	J.M.H.	42	Neg. 100 per min.	"	"	B.P. 170/118
73	T.J.K.	42	T 1–2–3 inv.	RST 2	RST 2	B.P. 190/116
			Effort Syndrome			
74	A.G.B.	23	55 per min.	T 2	T 2	
75	L.S.M.	20	Neg. 100 per min.	T 2	T 2	
76	A.N.R.	43	" 100 "	T 2	None	O_2 stopped at 5 min. collapsed
77	E.M.T.	27	" 84 "	RST 2–3, T 1–2–3	RST 2, T 1–2–3–4	
78	D.A.D.	35	" 120 "	None	None	
79	J.J.B.	25	" 110 "	RST 2–4	RST 2–3–4, T 1–2–3	
80	O.L.B.	30	" 88 "	T 1	T 1	
81	J.W.C.	20	" 96 "	RST 2–3, T 2	RST 2–3	
			Miscellaneous			
82	L.M.S.	21	45 per min.; many prem. vent. beats, T 1 flat	T 1	T 1	O_2 stopped at 15 min.; collapsed (bradycardia)
83	J.W.W.	34	105 per min., T 1–2–3–4 inv.	T 4	None	Cong. dilation, pulmonary artery
84	Miss D.R.	24	Neg.	RST 2–3, T 2	RST 2–3, T 2	Funnel chest

CORONARY HEART DISEASE. There were 20 patients with coronary heart disease, 8 of whom had previously suffered coronary artery occlusion. The ages ranged from 35 to 66 years. Thirteen patients developed abnormal ECG after the "two-step" test and this evidence of coronary insufficiency was substantiated by the 10% oxygen test (Table 2).

In every patient in whom the "electrocardiogram after the two-step"

was normal the 10% oxygen test was normal, except possibly in Patient R.S.H. (Case 42) in whom a nodal rhythm appeared after breathing low oxygen. In this instance the 60 year old man collapsed after only 6 minutes of the diminished oxygen supply.

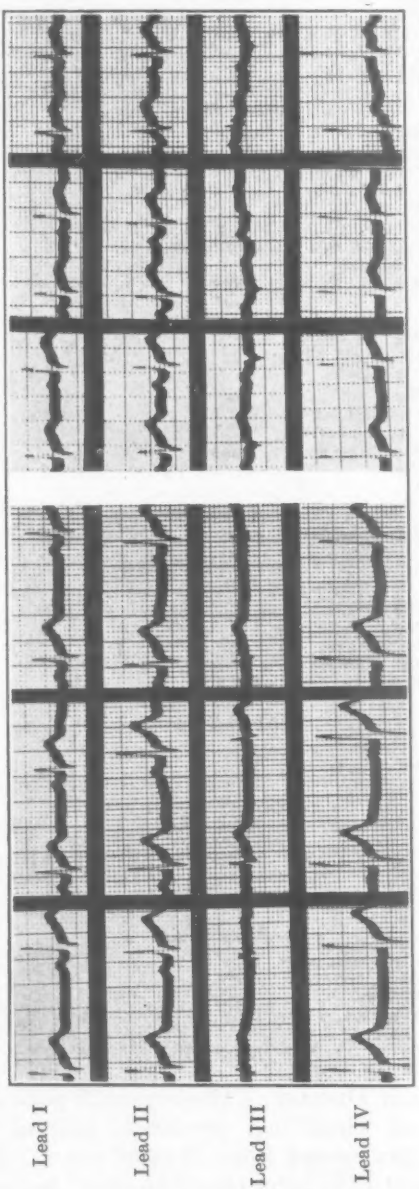

FIG. 2.—M.S.A., male, age 21. Normal subject. Control ECG negative and no change following the "2-step" exercise. Similarly no change in the ECG on breathing; 10% oxygen for 20 minutes.

Occasionally the results of the "two-step" were positive whereas the 10% oxygen was negative. Clinical experience proved the findings of the "two-step" to be correct. In Patient R.S.K. (Case 45) a

Q 4 appeared after the "two-step" and not after the 10% oxygen. This marine corps officer had suffered an acute coronary artery occlusion a few years before and was being reëxamined for possible return to active duty. He was found unfit. Patient W.H.S. (Case 42) was examined because of an anginal syndrome. Physical examination and the control ECG were normal. However, the "electrocardiogram after two-step" exercise revealed significant T 1 and T 2 changes and so a diagnosis of coronary heart disease was made, although the 10% oxygen test was normal. That the result of the former test was truly indicative of coronary insufficiency was proven 3 months later when the man was admitted to the Naval Hospital because of severe chest pain with fever, leukocytosis and increased sedimentation rate. It is significant that the ECG in this attack was similar to that following the "two-step."

In 2 other patients clinical experience confirmed the value of the "electrocardiogram after the two-step" as a test of latent coronary insufficiency. The patients, H.A.K. (Case 44) (Fig. 3*a*) and L.P.S. (Case 50) first entered the Naval Hospital because of severe coronary heart attacks. Months later, after the ECG had returned to practically normal and there had been clinical improvement, the "electrocardiogram after "two-step" was taken and found to be positive (Fig. 3, *b*). The ECG revealed changes similar to those seen in the actual heart attacks.[11]

The control ECG of 7 of the patients with coronary heart disease were normal and 4 became definitely abnormal following the "two-step." Hence, the test is of particular value for detecting coronary insufficiency when it is latent.

Although many of the coronary heart patients were definitely ill, there was not one bad reaction to the "two-step" test. Patient H. S. (Case 52) had actually suffered a coronary occlusion 2 months before. He stood the "two-step" very well, yet when the 10% oxygen test was performed he became so completely exhausted that it was stopped before the time was up. Two other patients collapsed during the oxygen test, R.S.H. (Case 42), W.H.S. (Case 49), and, in one other, F.O.H. (Case 43), severe nausea and dyspnea appeared in 5 minutes. It is thus clear that the 10% oxygen is a severe task for moderately sick cardiac patients whereas the "two-step" is readily performed.

Summarizing these cases, the "electrocardiogram after the two-step test" is a measure of coronary insufficiency or anoxemia of the heart muscle as proven by the 10% oxygen test and as shown by long clinical experience. It is particularly useful when the control ECG is normal. The exercise is harmless.

VALVULAR HEART DISEASE. Thirteen patients suffering from chronic cardiac valvular disease, with mitral or aortic valve involvement (ages 20 to 39 years), were tested. There were 10 with mitral disease alone, 1 pure aortic, and 2 with combined lesions. Here, again, whenever the "electrocardiogram after the two-step" was abnormal the ECG in the 10% oxygen test confirmed this evidence of coronary insufficiency. This was true in 7 cases.

Two patients with valvular heart disease whose "electrocardiograms after the two-step" exercise were positive possessed normal control ECG. This again emphasizes the usefulness of this test for latent coronary insufficiency.

Not one of these 13 ambulatory patients was affected in any way by the "two-step" exercise but 3 suffered severe reactions in breathing 10% oxygen. In patients suffering from chronic cardiac valvular disease the 10% oxygen test requires a close watch.

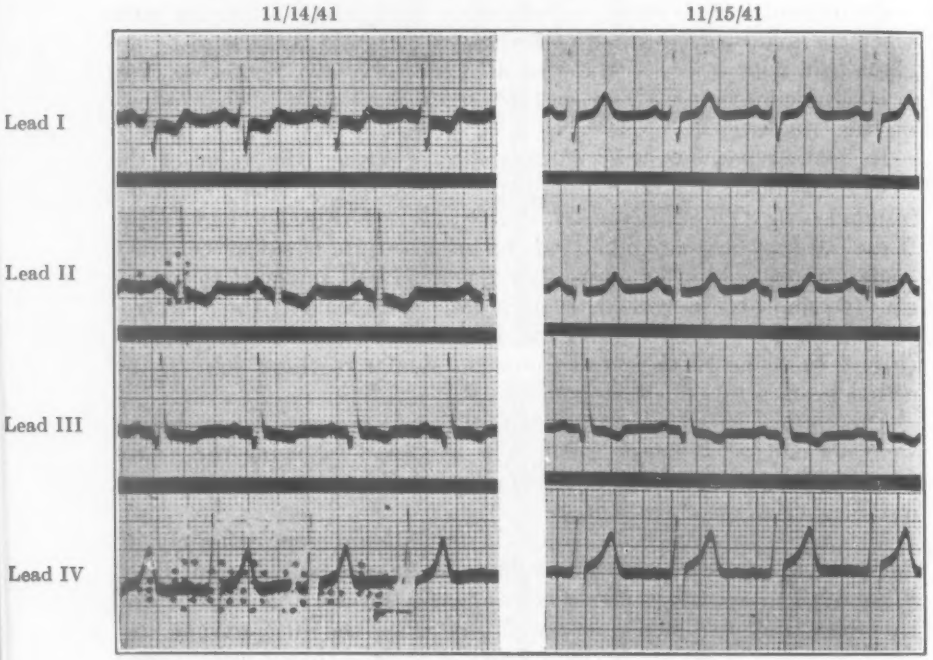

FIG. 3a.—H.A.K., age 54, U. S. N. Acute coronary insufficiency. Coronary heart disease. An attack of severe chest pain Nov. 14, 1941, for which immediate hospitalization was required. The ECG disclosed RST depressions and T-wave inversions in Leads I and II. By the next day, concomitant with the subsidence of the pain, the tracing had returned to normal.

It is to be expected that patients suffering from mitral stenosis frequently disclose coronary insufficiency following the "two-step," for in a "tight mitral" not enough blood reaches the left ventricle. Consequently, when this chamber contracts, only a small quantity of blood is ejected into the aorta and an insufficient quantity of blood enters the coronary arteries, resulting in myocardial anoxemia. The RST depressions and T-wave inversions are presumably the consequence of this muscle anoxemia. In aortic insufficiency a similar mechanism may be present, for, because of the regurgitation back to the left ventricle, an inadequate quantity of blood enters the coronary arteries.

In valvular heart disease the ordinary ECG is so frequently normal that the ECG after the "two-step" exercise is of particular value for testing for anoxemia of the heart muscle on effort.

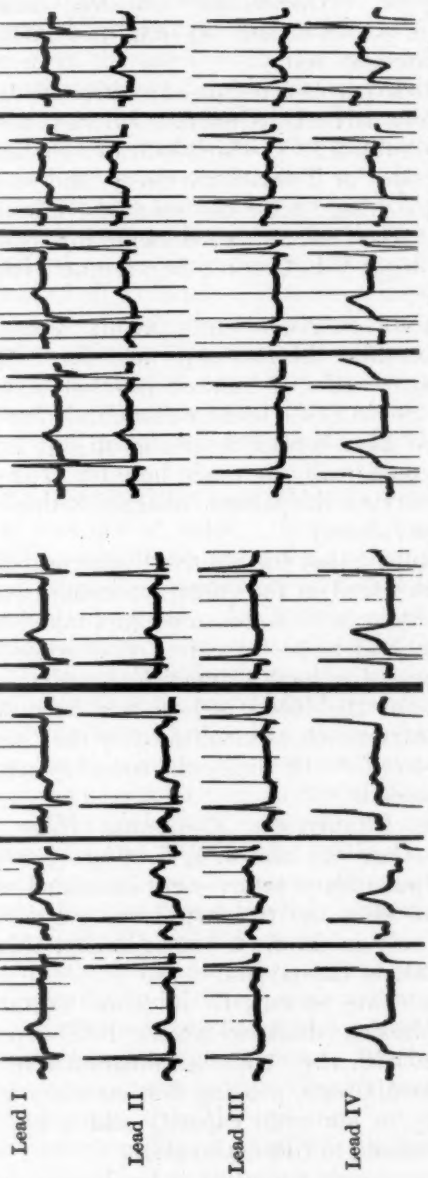

FIG. 3b.—H. A. K., age 54, U. S. N. Coronary insufficiency. Coronary heart disease. Control electrocardiogram normal. Immediately following "2-step" exercise marked depression of the RST segment in all leads and inversion of T 2 and 3 occur. At 2 minutes, the T wave becomes semi-inverted. Return to normal in 8 minutes. After breathing 10% oxygen there were marked depressions of the RST segments and inversion of the T wave in Leads I, II and IV.

HYPERTENSION. There were 7 patients (41 to 64 years of age) with the diagnosis of "arterial hypertension" in whom both the "electrocardiogram after the two-step" and the 10% oxygen tests were performed. In this group also it was true that when the "two-step"

was negative there were no ECG changes on breathing 10% oxygen. In the one patient who demonstrated RST depressions in Lead II of the ECG after the exercise exactly similar results were obtained on breathing low oxygen. Whereas the "two-step" caused no ill-effects, the first 2 patients (Cases 67 and 68) could not finish the 20 minutes for the 10% "anoxemia" test.

One patient with hypertension showed positive changes after the test. However, 3 subjects, J.H.S.D. (Case 69), J.R.E. (Case 71) and T.J.K. (Case 73) revealed control ECG which indicated coronary insufficiency, *i. e.*, RST depressions or T-wave inversions, and so it is no wonder that there was no change after the exercise. [Similar observations were made in D.A.D. (Case 38), a man suffering with coronary heart disease, and in subject V.L.A. (Case 55), a man with valvular heart disease.]

Effort Syndrome or Neurocirculatory Asthenia. Both the "electrocardiogram after the two-step" and the 10% anoxemia test were performed in 8 cases of marked neurocirculatory asthenia or effort syndrome. Seven ECGs became abnormal after the "two-step." The anoxemia test gave similar results in all but 1 case (Case 76). (No comparison could really be made here for after only 5 minutes of breathing 10% oxygen the patient collapsed with all the evidence of peripheral vascular failure.)

We are of the opinion that the positive "electrocardiogram after the two-step" so often found in the effort syndrome patient is evidence that the small or hypoplastic heart sometimes found in such a person is constitutionally inadequate to carry on exertion. These people tire on effort because they have a diminished cardiac output[17] and the oxygen saturation of the blood is low[3] and because they develop anoxemia of the heart muscle as manifested by the "electrocardiogram following the two-step."[10] Of course the coronary arteries themselves may be entirely normal.

Miscellaneous Conditions. *Congenital Heart Disease.* Two patients, L.M.S. (Case 82) and J.W.W. (Case 83) with congenital dilatation of the pulmonary artery were examined and in both the "electrocardiogram after the two-step" was positive, but the 10% test was positive only in the first. Incidentally, this man collapsed during the inhalation of the oxygen.

Chest Deformity. One patient, D. R. (Case 84), a woman with a funnel-shaped depression, disclosed similar RST depressions and T-wave inversions in both the "electrocardiogram after the two-step" and the 10% anoxemia tests, proving that coronary insufficiency was present. Clinically, a low vital capacity and a low breath-holding time added confirmation to this explanation.

Comment. As previously remarked, it has been suspected for a long time that the RST depression and T-wave inversion following exercise were caused by anoxemia of the heart muscle, *i. e.*, the coronary circulation was not responsive to the demand of the heart muscle for oxygen.[2,13,16] We have definitely proved it. Our results show an uncanny correlation between the ECG following the "two-step"

exercise and that obtained after breathing diminished oxygen, *i. e.*, 10% oxygen.

It is interesting that 10% oxygen, rather than 11 or 9%, produces exactly the same changes in the ECG as the "two-step," exercise. We have experimented with oxygen from 8.5 to 12% and have found that 10% oxygen gave the same results as the "two-step" whereas anything less than this produced more marked ECG changes (and in addition was too dangerous for patients suffering from cardiac and pulmonary disease) and concentrations of oxygen higher than 10% did not produce sufficient anoxemia of the heart muscle.

The significance of exercise tests by earlier investigators was obscure because the amount of work performed by the individual being tested was not standardized. One investigator exercised the subject to fatigue, another only half as much. This is an important consideration because it is known that even a normal man may show ECG changes if allowed to exercise long enough.[13] Hence, the "two-step" exercise has been standardized according to sex, age and weight. This, too, is the first time that the ECG changes have been related to a definite amount of work which will not produce ECG abnormalities in a normal person.

Riseman[16] and his co-workers used the "two-step" exercise and concluded that it was not of value. However, they regarded any change in the RST as significant, not realizing that the RST segment must be depressed below the isoelectric level before the ECG response should be diagnosed abnormal. In healthy persons there is frequently an elevation of the RST which may drop to the isoelectric level after exercise. These workers furthermore did not adhere to the technique we have described in our original reports.[8,15] Instead of a definite number of climbs as obtained from the table, performed in a definite time, *i. e.*, in 1½ minutes, these investigators permitted their patients suffering from angina pectoris to choose their own pace and to continue as long as they could walk until pain set in.

Similarly, Laurentius and Klopfleisch,[5] in the German army, take the ECG after bending the knees 25 times. Here again the amount of work is not standardized and knee-bending is an unaccustomed type of activity for a patient with heart disease.

It has been pointed out that an atmosphere of ordinary quiet must be maintained during the test. Excitement and apprehension should be avoided. An ordinary conversational tone and attitude are desired. Too much quiet makes the examinee nervous. We have definitely seen intense nervousness in a patient produce changes that were not present in the "electrocardiogram after the two-step" or on breathing 10% oxygen when the patient was at ease and this has been reported in the literature.[7]

The results of the "electrocardiogram after the two-step" correlate with clinical findings and follow-up.[9,11,12,13,14] We have already given illustrations but there are many others, just as dramatic, which were not included, because in this report we presented only cases in which the patient took the 10% oxygen test as well as the "electrocardiogram

after the two-step." We have had numerous other examples that prove that positive changes in the "electrocardiogram after the two-step" indicate coronary insufficiency and may presage a serious attack of coronary heart disease. For example, a 63 year old officer was examined for some minor complaints. Examination was essentially negative but because of a positive "electrocardiogram after the two-step" the diagnosis of coronary insufficiency was made. Three months later he was admitted to the hospital because of shortness of breath and easy fatigability. The sedimentation rate was increased and the ECG at rest disclosed evidence of myocardial infarction. Another officer was thoroughly examined because he complained of precordial pain. All results were negative including the control ECG at rest. However, the "electrocardiogram after the two-step" was positive, *i. e.*, T1 became inverted; hence a diagnosis of coronary heart disease with coronary insufficiency was made. The basal metabolism was low and thyroid therapy was instituted. Because of its complete success in entirely alleviating the officer's complaint, the diagnosis of hypothyroidism was made and a doubt arose as to the presence of any coronary heart disease. Three months later, however, the patient sustained a severe attack of chest pain for which he was hospitalized for many weeks. Whereas his resting control ECG had always been normal it now presented deeply inverted T waves. The temperature was elevated, the blood count showed a moderate leukocytosis and the sedimentation rate was rapid. In other words, myocardial infarction on the basis of coronary heart disease was the cause of the patient's disability. Altogether, then, a long clinical experience has proven the value of the test for demonstrating diminished function of the heart and coronary insufficiency. This test meets the requirements expressed by Paul D. White,[19] "A simple test is less apt to strain unaccustomed muscles of the subject, less apt to exhaust prematurely a person not in good physical training and more convenient and practical to execute. In fact, such simple exertion as enters into the routine daily life of the patient is best of all."

There is a military application of the "electrocardiogram after the two-step" test. The question of the presence of heart disease or evaluation of cardiac function arises frequently since thousands of men are examined daily. Many officers in the armed forces are 40 or over, an age in which coronary insufficiency is common.[5] Military personnel work under extreme mental and physical strain and are often exposed to a decrease in oxygen supply, so these tests are of particular value. Athletes,[4] soldiers,[18] and fliers[1] may appear in the pink of condition and yet die suddenly under strain. In these men myocardial infarction is found at autopsy as a result of coronary insufficiency. It is therefore suggested that the test be applied to all applicants for the Navy during yearly examination, examinations for promotion, examinations for recall to active service, etc.

Summary. An experience gained over many years has proven the practical value of the "electrocardiogram following the two-step exercise" in 3 ways: *First*, the blood pressure and pulse response

indicate circulatory fitness by a standardized measurement of vasomotor response. *Second,* the ECG changes are an indication of the oxygen supply of the heart muscle itself. *Third,* the control ECG reveals the presence of arrhythmias and is an indication of the condition of the myocardium with the patient at rest.

The test is of importance in differentiating functional from organic heart disease, particularly when physical examination, Roentgen ray film, fluoroscopy and ECG are negative.

Positive changes in the ECG after the "two-step" exercise indicate anoxemia of the heart muscle or coronary insufficiency. Both this test and the 10% oxygen anoxemia test were performed on every person considered in this report. The ECG changes corresponded almost exactly in both tests.

The exercise must be standardized for age and weight since changes occur in normal people if the effort is excessive. Tables giving the number of trips to be performed by normals have been published. In normal persons the blood pressure and pulse return to within 10 points of resting levels in 1½ minutes. The following changes in the "electrocardiogram after the two-step" are considered abnormal: A depression of the RST segment of more than 0.5 mm. in any lead, a change from an upright T wave to an isoelectric (flat) or inverted T wave or T-wave changes in the opposite direction.

In patients with coronary heart disease the test is of particular value in detecting coronary insufficiency when it is latent.

In valvular heart disease the test discloses the state of cardiac function and whether the cardiac output is adequate for the coronary arteries.

In patients with hypertension the control ECG often shows evidence of coronary insufficiency and therefore may not change after exercise. There is a lag in return of the blood pressure and pulse following the "two-step" exercise in effort syndrome (neurocirculatory asthenia) and the ECG gives evidence of anoxemia of the heart muscle following exercise. In this syndrome we believe there is a congenitally small, hypoplastic heart which is inadequate on effort.

In chest deformities and in congenital heart disease the "electrocardiogram after the two-step" is valuable.

An upper respiratory infection, lung disease, gastro-enteritis, fatigue and lack of sleep may produce abnormal results.

The "electrocardiogram after the two-step" is a short, harmless and practical test. It is suggested that it should be a routine procedure in men over 40 in the military service and also for eliminating the unfit for special services where unusual physical and mental strain are experienced, as in aviation, submarine, raider forces, and so on.

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MORPHOLOGIC OBLITERATION OF CHRONIC MYELOID LEUKEMIA BY ACTIVE TUBERCULOSIS

REPORT OF A CASE

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A PATIENT with chronic myeloid leukemia in whom the course and pathologic findings were greatly altered by fatal tuberculosis occurring after the diagnosis of leukemia had been established, has been reported by Ulrich and Parks.[5] Autopsy of their patient revealed very little morphologic evidence of leukemia in the organs, although there had been no doubt of the diagnosis during life.

Since there is still considerable disagreement[6] concerning the effect of tuberculosis in particular and infection in general on the course of chronic leukemia, the following case is reported. This case is similar to that of Ulrich and Parks, but may be of greater interest because the leukemia was observed for a longer period of time and the time of onset of the active tuberculosis could be dated exactly.

Case Study. J. S., a 36 year old white male, entered the Lakeside Hospital in November, 1935, with a diagnosis of chronic myeloid leukemia. The diagnosis had been established at another hospital in January, 1935. At that time the spleen was enlarged and the white blood count was 385,000. He was given Roentgen ray therapy to the spleen and a total thyroidectomy was done because of an elevated basal metabolic rate. Following discharge from the hospital he felt well and was symptom-free when he entered the Lakeside

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Hospital for study. The past history and family history were not important. Fowler's solution had been given intermittently before entry to the hospital.

The physical examination was entirely negative except for slight enlargement of the liver and spleen, both of which were just palpable at the costal margins on deep inspiration. The temperature was 37.2° C.

The red blood count was 4,500,000 per c.mm., with 91% (14.2 gm.) hemoglobin, and the white blood count was 11,500 per c.mm. with 66% polymorphonuclears, 2% myelocytes, 1% eosinophils, 24% basophils, 2% lymphocytes, and 2% monocytes. The blood platelets were abundant. The Kline exclusion test, stool examination, and urine examination were negative. The blood urea nitrogen was 8.3 mg. per 100 cc., blood uric acid 2.9 mg. per 100 cc., and blood cholesterol 162 mg. per 100 cc.

During the hospital stay of 6 days, he was asymptomatic. He received 9 to 15 drops of Fowler's solution daily and this medication was continued after discharge.

During the next 4½ years, from November, 1935, until his death in March, 1940, he was admitted to the Lakeside Hospital on 8 occasions and in the interims was followed in the Out-Patient Department. During this time the white blood count varied from 6000 to 170,000 per c.mm., the hemoglobin from 60% (9.4 gm. per 100 cc.) to 90% (14.4 gm. per 100 cc.), myelocytes from 0 to 54%, and myeloblasts from 0 to 10%. The adult polymorphonuclear neutrophil was the predominant cell throughout except for one period when the basophils rose to high levels. Normoblasts were present irregularly in small numbers and an occasional cell undergoing mitosis was found in the peripheral blood.

During the entire 4½ years, he was treated intermittently with Fowler's solution in doses of 9 to 24 minims daily. On 3 occasions Roentgen ray therapy was given when early symptoms of arsenic poisoning made the withdrawal of Fowler's solution necessary. In every instance, there was a good response to both arsenic and Roentgen ray with decrease in the total number of white blood cells, myelocytes, and myeloblasts and increase in hemoglobin. The platelets remained abundant throughout.

Five months before his death, his disease was complicated by the appearance of pleurisy. Immediately following what appeared to be an ordinary head cold, he developed severe pleuritic pain in the left chest accompanied by an audible friction and followed by clinical and Roentgen ray findings of pleural effusion. His temperature became elevated and from then until death ranged between 38° and 40° C. Frequent Roentgen ray examinations showed increase in the pleural effusion and subsequent parenchymal involvement of the left lung field. It was considered possible that the entire pulmonary picture might be the result of leukemic infiltration, but the opinion of most observers that tuberculosis was responsible was confirmed when fluid from the left chest was injected into guinea pigs and produced tuberculosis in those animals. Repeated examinations of pleural exudate, sputum, and gastric washings failed to reveal the presence of acid-fast organisms.

During the final 4 weeks of his illness, the white blood count fell to normal and then to subnormal levels. On 1 occasion, it was as low as 2000 per c.mm. The percentage of immature cells decreased, the myelocytes varying from 1 to 10%, and myeloblasts from 0 to 2%. During this final hospital admission, he received Fowler's solution in doses which were generally smaller than he had been receiving before. The average dose during this time was 9 to 12 minims daily. Only for a few days were larger doses given and on 2 occasions, for periods of 1 month each, the drug was discontinued entirely without rapid rise in the white blood count or other evidence of relapse. No Roentgen ray therapy had been given for 8 months before death.

During the 4½ years that he was observed, the liver and spleen had gradually increased in size. Just before death the essential physical findings included an enlarged liver palpable 2 cm. below the costal margin, the spleen palpable 10 cm. below the costal margin, and signs of left pleural effusion. On the day of death, the white blood count was 12,850 per c.mm. The differential blood

count revealed 82% polymorphonuclear neutrophils, 9% myelocytes, 2% myeloblasts, 5% basophils, 1% lymphocytes, and 1% monocytes. The hemoglobin was 70% (10.9 gm. per 100 cc.) and the blood platelets were abundant.

An autopsy was performed at the Institute of Pathology, Western Reserve University, by Dr. H. K. Giffen, and the principal pathologic diagnoses were as follows: Miliary tuberculosis of the lungs, liver, spleen, kidneys, bone marrow, lymph nodes, and adrenal glands: active, progressive, primary tuberculosis, upper lobe of left lung and hilic lymph nodes: myeloid metaplasia of bone marrow: splenomegaly (910 gm.): hepatomegaly (2470 gm.): chronic adhesive fibrous pleurisy, left: hydrothorax, right (2500 cc.): ascites (2300 cc.): Culture of heart's blood: no growth.

Extensive tuberculosis was found in the upper lobe of the left lung. Elsewhere in the lungs and in the other organs listed above, scattered miliary tubercles were found. Bone marrow sections from sternum, rib, humerus, vertebra, femur, and tibia showed only myeloid hyperplasia and metaplasia. There were increased numbers of myeloid elements without marked increase in immature forms and all the marrow contained adequate numbers of red blood elements and megakaryocytes. Leukemic infiltration in other organs was completely absent, even in the spleen which weighed 910 gm.

Comment. The tendency for the blood picture to revert towards normal coincident with the progress of the tuberculosis was an interesting feature of this case. Because of the fact that Fowler's solution was administered intermittently, it is impossible to say whether this change was due entirely to the drug or to the infection. It was felt, however, that the smaller doses of the drug would not be expected to produce such a profound effect on the blood and that the infection probably played an important part.

The relationship between leukemia and tuberculosis has been a subject for discussion over a period of 50 years. In various summaries,[1–4] and in numerous case reports the following hypotheses have been advanced to explain the varying clinical and pathologic pictures:

A. Preëxisting leukemia is modified by superimposed active tuberculosis.

B. Primary active tuberculosis produces a leukemoid blood picture.

C. The 2 diseases may coëxist without much effect on the clinical or pathologic features of either one.

The individual cases reported in the literature varied widely in their outstanding clinical and pathologic features. However, they may be classified roughly into the following groups:

1. Apparent leukemia observed for a considerable period of time in patients susbsequently developing tuberculosis: (*a*) without change in the expected clinical or pathologic signs of leukemia; (*b*) with modification towards normal of the expected clinical or pathologic signs of leukemia; (*c*) with complete or almost complete disappearance of all clinical and pathologic signs of leukemia.

2. Coëxistence of leukemia or leukemoid blood picture with active tuberculosis at the time the patient is first observed with development of *a*, *b*, or *c* as under No. 1 above.

The case reported here belongs in Group 1 *c* The patient was followed continuously for 4½ years before active tuberculosis developed. During that time there was no doubt about the diagnosis of

chronic myeloid leukemia and not until the tuberculosis became advanced was there any significant change in the signs of leukemia.

It may be significant that we are unable to find any cases in the literature of active chronic tuberculosis observed over a considerable period of time which subsequently developed clinical or pathologic evidence of true leukemia. Those authors who defend the hypothesis that primary active tuberculosis may produce a leukemoid blood picture were unable to give unequivocal evidence of active tuberculosis antedating changes observed in the blood. They inferred from the patient's history that such was the case but positive evidence was lacking. They were never able to state definitely that leukemia had not antedated the tuberculosis.

Summary. The case reported here is presented as further evidence that tuberculosis may have a profound influence upon the clinical and pathologic features of chronic myeloid leukemia. It is probable that some factor, produced by infection with tuberculosis, altered the course of the leukemia and caused the reticulo-endothelial system to revert towards normal. In such cases, one is unable to find definite evidence of leukemia at autopsy, although the diagnosis has been established beyond doubt during life. If the mechanism of this process were known, the pathogenesis of leukemia might be more readily discernible.

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ALLERGIC AGRANULOCYTOSIS WITH COMPLICATIONS

Case Report

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There is an old adage in medicine, "Never despair of the young." This case is presented because it reiterates this axiom.

The fact that this patient survived these 8 conditions, namely, acute catarrhal fever, lobar pneumonia, agranulocytic angina, acute myocarditis, acute otitis media, bilateral suppurating cervical adenitis and pyelonephritis, concurrently and intercurrently, any of which could have proved fatal, makes the case somewhat of a medical menagerie.

The complications and sequelæ and progress of the case also are of interest, because it emphasizes some of the complications which may arise when infection is present with the function of the hematopoietic systems disturbed.

Report of Case. This 18 year old white male was admitted to the hospital on 2/28/43, with a diagnosis of acute catarrhal fever. His chief complaints were sore throat and a head cold, duration of 4 days.

The *past history* was irrelevant, except for a tonsillectomy at 7 years of age and a history of hives in the summer, the usual childhood diseases, and pneumonia at 7 years.

The *family history* shows an allergic background (mother suffered from hay fever, sick headaches, colitis and chronic sinus trouble).

Physical examination revealed a well developed and nourished white male 68 inches tall, weighing 149 pounds, apparently not acutely ill. His temperature was 103° F., pulse 135, respiration 35. General physical examination was negative except for a slightly stuffy wet nose, injected throat and posterior pharynx.

He was placed on symptomatic treatment, acetylsalicylic acid 10 grains being the only drug taken internally. Since his temperature receded to normal and he felt well in 2 days, the acetylsalicylic acid was then discontinued. On 3/3/43, the patient's temperature rose to 103° F., accompanied by pain in the right thorax and a productive cough. Roentgen ray and physical findings revealed a lobar pneumonia of the lower portion of the upper right lobe. He was placed on sulfadiazine with 2 gm. for the initial dose and 1 gm. every 4 hours. The red blood count was within normal limits. The white blood count showed 20,000 white cells with an increase in polymorphonuclear leukocytes.

The temperature was fluctuant but gradually receded until 3/12/43, when it dropped to normal. The findings in the chest were somewhat diminished but still revealed an unresolved pneumonia of the upper right lobe, which was confirmed by Roentgen ray. The dosage of sulfadiazine was reduced to ½ gm. every 4 hours on 3/13/43. He continued to have a temperature which ranged from normal to 99.6° F. with coarse râles in the upper right thorax and at the base.

On 3/22/43, 19 days after the beginning of sulfadiazine therapy, his temperature became normal and the drug was discontinued after a total consumption of 27 gm. Two days later his blood count showed 5,130,000 R.B.C. and 4550 W.B.C.

Convalescence was uneventful until 3/26/43, at which time he developed a sore throat, slightly tender cervical lymph nodes and pain in the right thorax, productive cough, friction rub, and râles in the right thorax at the base. Sulfadiazine was again started. On 3/29/43, the cervical lymph nodes became more swollen and tender, and the throat symptoms became worse. Sulfadiazine was discontinued after consumption of 4 gm. and granulocytopenia was suspected. The white blood count was 1950, 97% lymphocytes, and 3% monocytes, showing a complete agranulocytosis. His temperature was 104° F.

The diagnosis was changed to malignant granulocytopenia. Small frequent transfusions of 300 cc. of citrated blood daily and 20 cc. of pentnucleotide intramuscularly twice daily was instituted. On 4/1/43, his temperature was 99° F. in the morning but rose to 104° F. at 3 P.M. He became irrational, the cervical lymph nodes became more swollen, the throat became edematous with white ulcerations present on the tonsillar pillars and soft palate. On 4/2/43, pentnucleotide was increased to 40 cc. intramuscularly twice daily and the patient was given 500 cc. of citrated blood intravenously. Appearing to be failing gradually, his temperature being 100.6° F., pulse 130 and thready, he was placed on digitalis and put in an oxygen tent.

On 4/3/43, his course was febrile, the blood count showing 2150 W.B.C., with a slight return of immature granulocytes. Citrated blood (300 cc.) was given intravenously. One-half hour later he had a severe chill and his temperature rose to 107° F. A white blood count was taken ½ hour later and revealed 8700 cells. The chest showed impaired resonance, at both bases of the lungs with considerable bubbling râles present. He was expectorating blood-tinged pus which showed numerous short chain streptococci. He complained of pain in the left chest.

On 4/4/43, his temperature was receding, he appeared much improved and

was orientated in all spheres. The Roentgen ray showed unresolved pneumonia in the right upper lobe; right cardiac decompensation, and the ECG showed evidence of widespread myocardial damage. The cervical lymph nodes swelling was less pronounced and less tender, throat ulcers were better, temperature was 100° F; moist râles were present in both bases, more marked on the right, the heart rate was rapid and respiration was increased. Fluids were restricted to 2000 cc. daily, intake and output recorded, and 1 cc. of concentrated liver extract was given in conjunction with the above therapy.

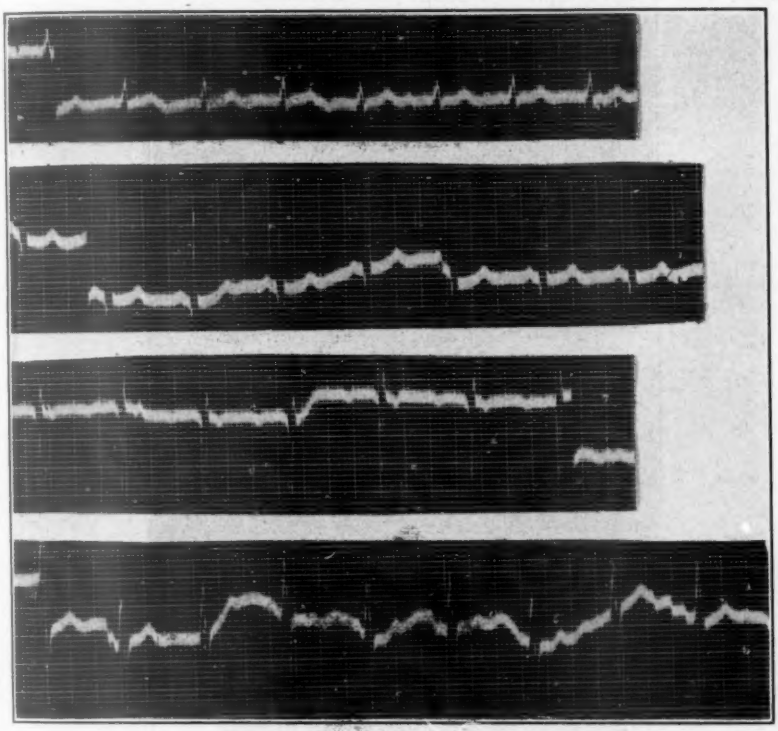

FIG. 1

He appeared much improved on 4/5/43 (Fig. 1), and was taking nourishment. The W.B.C. was 24,000, segments 43%, bands 26%, juveniles 1%, myelocytes 1%, monocytes 5%, lymphocytes 23%, and the R.B.C. was 4,150,000. An acute otitis media developed on the right side and began discharging pus from the ear on 4/8/43. The cervical lymph nodes became woody to palpation, the heart rate and rhythm and tone became normal and pentnucleotide therapy was discontinued on this date. His general condition and blood count gradually improved but the angina persisted, and the temperature became elevated. On 4/15/43 Roentgen ray therapy was instituted, 100 R being applied to both sides of the neck. On 4/16/43, the patient was unable to swallow, fluids returning through the nose when he attempted to swallow. The left side of the neck became fluctuant and a large amount of thick yellowish non-odorous pus was evacuated surgically. The W.B.C. rose to 51,000 with a polymorphonuclear leukocytosis predominating. When the right side of the neck was surgically drained on 4/20/43, the temperature and elevated blood count receded and the otitis media cleared up. The blood and lungs were normal on 4/23/43, with the exception of a few coarse râles in the right

base. These findings were confirmed by Roentgen ray examination, but the ECG showed the myocardial damage to persist (Fig. 2).

On 4/28/43, there was a sharp rise in temperature and a septic course developed accompanied by pain in the abdomen and flanks. The urine for the first time showed albumin and W.B.C. in increased numbers. Roentgen films of spine, psoas muscles, heart and lungs were negative. The urinalysis continued to show from 40 to 100 mg. per 100 cc. albumin, 15 to 40 W.B.C per high-power field, and many erythrocytes and granular and hyaline casts. Diagnosis: Acute pyelonephritis. The W.B.C. has ranged from 8000 to 15,000 with a high lymphocyte count predominating.

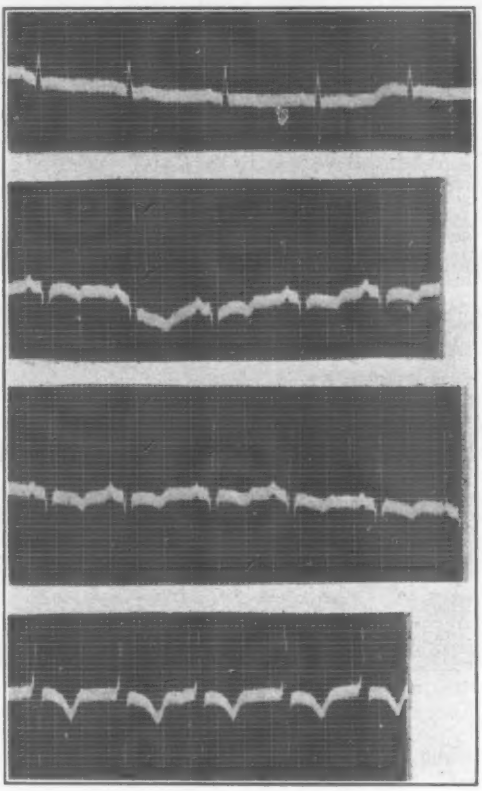

FIG. 2

The urinary findings and elevated temperature have gradually receded, by a watchful, waiting therapy consisting of fluids restricted to 2500 cc. daily, low protein, high carbohydrate diet and recorded intake and output. No drugs were given for fear of inciting the agranulocytosis again. Since 5/9/43, the patient's temperature has remained normal and the urinary findings have returned to normal.

The ECG of 5/24/43 (Fig. 3), reveals marked myocardial damage still present but shows improvement in its function. Subsequent tracings may show a greater return to normal than has been seen so far, as his myocardial damage is still recent. These tracings show a prolonged parenchymatous change of a degenerative nature and are not consistent with cardiac damage in pneumonia and acute infections.

The A–V node is not involved and there is a possibility of his other infections being accompanied by a latent rheumatic fever.
The blood picture has returned gradually to normal.*

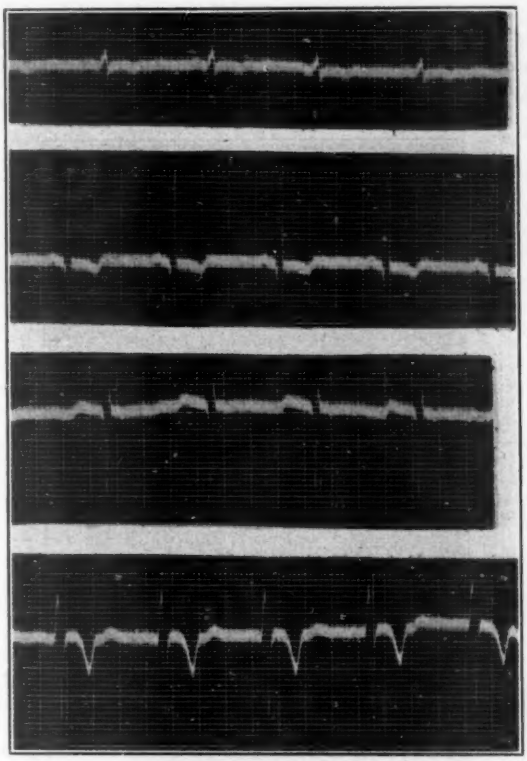

FIG. 3

Allergy as a Factor in Drug Toxicity and Granulocytopenia. When asymptomatic, an allergic person is in a state of equilibrium, but his hypersensitive tissues are analagous to a loaded gun or an electrical current. When the inciting allergens, which may be compared to the trigger or switch are encountered, this state of equilibrium may become disrupted and any of the shock tissues may become involved.

Thus, in our present day of synthetics and new drugs, allergy has assumed a larger field than the hay fever, urticaria and asthma of the past. "A person who is allergic to ordinary innocuous agents is apt to be more sensitive than normal to many or all toxic agents, which is well illustrated in agranulocytic angina. Patients with this condition are almost universally allergic to many substances."[10]

Rowe[15] is of the opinion that agranulocytic angina is due to allergy in the blood forming cells of the bone marrow.

Beckman[2] states that granulocytopenia occurs more frequently in children in the first 10 days of therapy and that true agranulocytosis

* Since submitting this paper for publication, another ECG was made on the patient, which revealed a normal tracing (Fig. 4).

with angina and the typical blood picture is rare, but such are being reported. Holten,[11] borrowing Quick's hypothesis, infers that it is an Arthus phenomenon localized to the leukopoietic part of the bone marrow.

Curry,[5] Levin and Bethell[14] have reported cases of agranulocytosis due to sulfadiazine, the latter reporting a fatal case. Conti[3] reported a fatal case due to sulfapyridine.

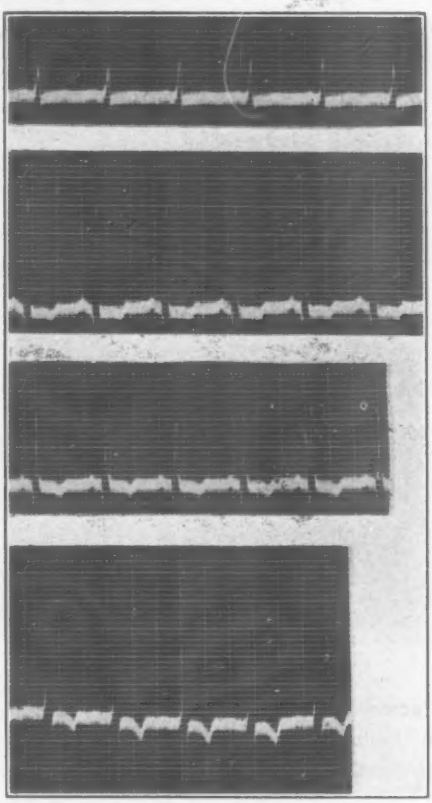

FIG. 4

Finland, Strauss and Peterson[8] reported a leukopenia incidence of 1.67% in a series of 776 cases who were taking sulfadiazine. Keefer[12] reported an incidence of 2% in his series of cases.

Flippin[9] states that depression of the bone marrow may occur at any time during the administration of sulfonamides but that no cases have developed within 12 days of such therapy.

Dameshek and Wolfson[6] believe that sulfathiazole is of value in combating the secondary sepsis in agranulocytosis and report 2 cases to substantiate their belief. Authorities on the subject, however, are not in accord with this idea and it is generally recognized that sulfonamides produce granulocytopenia and agranulocytosis by their toxic and allergic effect on the blood forming elements.

Sutliff *et al.*[18] found 1 fatal case of sulfonamide toxicity in every 2571 deaths from all causes, with a frequency of 1 sulfonamide death

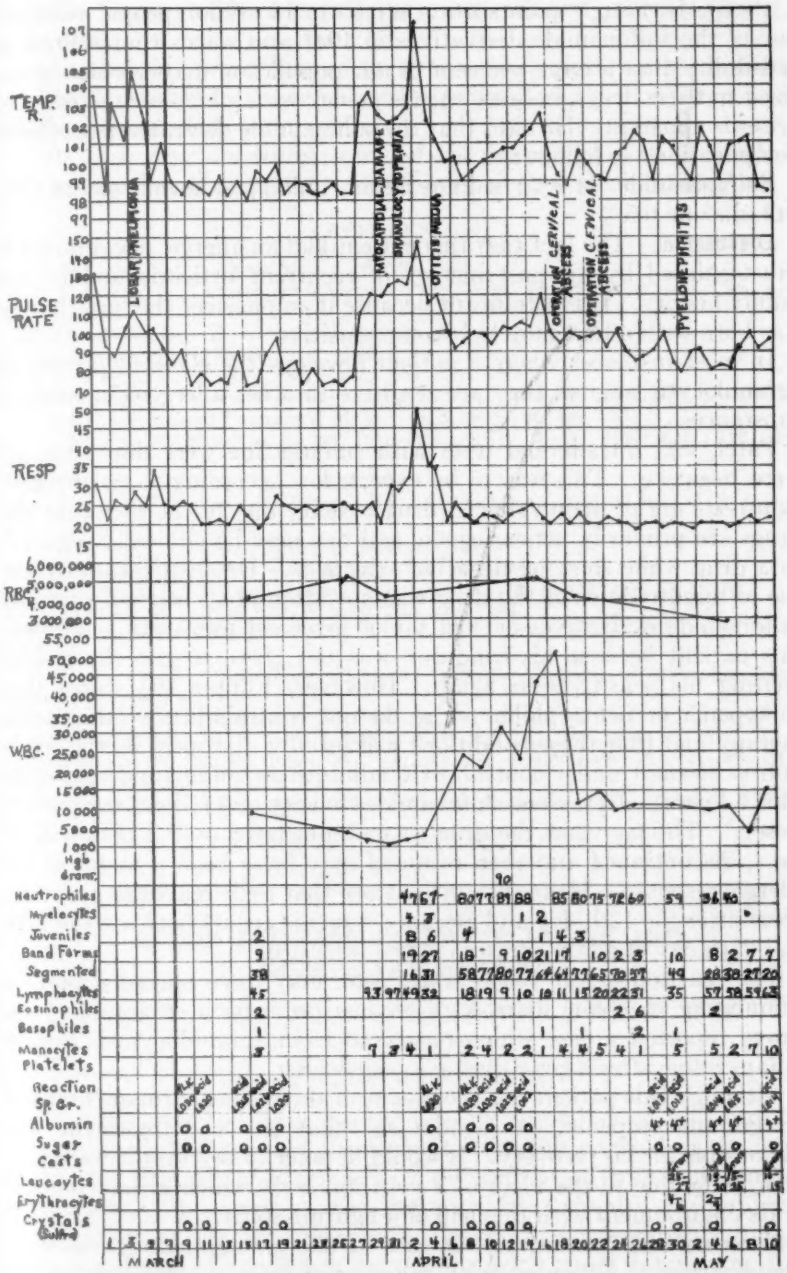

FIG. 5.—Diagrammatic presentation of course of events of a case of allergic agranulocytosis with complications, showing the relations of the complications to the temperature curve, blood-picture, urinary findings and sequence of events.

among 161 reported pneumonia deaths. He estimated that there was 1 sulfonamide death for every 1610 pneumonia cases in which a sulfa drug was employed.

Perrin H. Long[12a] points out that 10 to 15 million people received one of the sulfonamide derivatives in 1941 and warns that there is a possibility that a large per cent of our population may become sensitized to these drugs, because the frequency with which such sensitivity arises is apparent. He cites that the sulfonamide derivatives produced complications as follows:

Sulfanilamide 11.9%; sulfapyridine 15.9%; sulfathiazole 18.6%; sulfadiazine 6.5%.

Discussion. The fact that this patient had an allergic background is substantiated by his past history of recurrent urticaria and by his family history. It is significant because it emphasizes the fact that he was born with a tendency to become sensitive.

In most instances where a patient develops the classical picture of agranulocytic angina, they are sensitive to other allergens or noxious substances.

Patch and intradermal tests with sulfadiazine were done, but all were negative. This was to be expected. According to Sulzberger[19] skin tests are of little value in drug toxicity due to the fact that the drugs are primarily urticariogenic and one may be clinically sensitive to a drug while showing negative skin tests. Desensitization by the use of minute doses of the drug was not attempted, neither were any sulfonamide derivatives or coal tar or arsenical preparations allowed this patient because his condition was too grave to run the risk of inciting his sensitiveness again. However, Flippin (9) states that leukopenia or neutrophilia *per se* do not contraindicate sulfadiazine therapy and that these conditions will usually disappear as the infection is brought under control. He administers sulfonamides in cases with a history of previous sulfonamide toxicity and follows the patient closely. The fact that the drug was administered over a period of 19 days, discontinued and then resumed may have been a factor in the allergic response. Most authorities state that toxic reactions generally occur after the 12th day and granulocytopenia occurs between the 17th and 25th day of administration of the sulfa drug.

The reaction of the blood transfusion may have played a part in stimulating the bone marrow to resume production of granulocytes. Cross[4] reported a case which recovered from agranulocytosis due to sulfapyridine after a rigor during a transfusion.

Although this patient ran the gamut of the medical armamentarium for granulocytopenia, one cannot say that any one treatment was responsible for his recovery. It would be safer to say that it was more than likely due to the vigor of a youthful body which adjusted itself to its environment with the help of a fighting spirit.

Summary and Conclusions. A case of allergic agranulocytosis with complications is presented, with sulfadiazine being incriminated as the probable etiologic agent and the bone marrow serving as the trigger point of sensitivity, or shock tissue.

Charts, ECG tracings and Roentgen ray pictures of the case emphasize the various complications and sequelæ and progress of the case.

This case illustrates the grave complications which may arise from the sulfa therapy and is a warning to overdosing and prolonged use of a toxic drug.

Indiscriminate prescribing of these potentially toxic drugs should be guarded against in minor conditions especially to a person who has an allergic background.

This case also illustrates some of the many complications which may occur when the function of the hemopoietic system is disturbed.

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BLOOD DIASTASE VALUES IN MUMPS AND MUMPS PANCREATITIS

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Pancreatitis has been shown[8,10] to be accompanied by a prompt rise in blood diastase, and the estimation of this enzyme in the blood is used for diagnosis of pancreatitis in differentiation from acute surgical syndromes.[5] A survey of the literature has revealed no published observations of diastase values in the pancreatitis complicating mumps.

In the course of an epidemic at Camp Adair, from January to June 1943, the author saw over 600 cases of mumps. Occasional instances of pancreatitis were diagnosed clinically[1] among these cases, and the

diagnosis apparently verified by demonstrating elevated blood diastase values. It was noted that the elevated values would frequently be sustained for days, up to 3 weeks in one case, before dropping to normal, and that these sustained values were accompanied in most cases by symptoms and signs suggestive of continuing pancreatic disease.

The symptomatology suggestive of pancreatitis included a rise of temperature, leukocytosis, anorexia, nausea with or without vomiting, epigastric and left upper quadrant distress, severe abdominal distention, deep tenderness over the region of the pancreas, and occasional muscular rigidity of the epigastrium, left upper quadrant and left loin. Pain was vaguely localized to the upper abdomen, was frequently cramping, and was reproduced by deep pressure over the pancreas. Blood diastase values ran as high as 600 mg. per 100 cc.

Inasmuch as the salivary glands produce diastase, it seemed advisable to determine whether mumps, uncomplicated by pancreatitis, is accompanied by elevation of the blood diastase. Dunlop[4] found increased urinary diastase values in mumps, but Heifetz, Probstein and Gray[8] were unable to demonstrate a rise in blood diastase in a small series of cases. According to these authors, the only diseases of the salivary glands known to produce elevated blood diastase values are suppuration and ductal obstruction.

Method. Routine blood diastase values were taken on admission of a series of cases of mumps, and again prior to discharge. Except in occasional instances in which administrative reasons for discharge prevailed, patients with elevated diastase values were retained until these dropped to normal. During the course of illness, diastase values were also determined whenever symptomatology indicated the possibility of pancreatitis. Hospitalization time was 2 weeks as a minimum, and as much longer as signs or symptoms of any manifestation of mumps persisted.

All admission and discharge values are included in this analysis, and none disallowed. Diastase determinations other than those on admission and on discharge are not included in the tabulation.

TABLE 1.—DIASTASE VALUES IN MUMPS, ON ADMISSION AND DISCHARGE, OF A SERIES OF 89 CASES

Diastase values (mg. per 100 cc.)		No. on admission	No. on discharge
Subnormal, below 60		3 (3½%)	16 (20%)
Normal, 60-180		20 (23½%)	57 (71%)
Above normal		62 (73%)	7 (9%)
180-300	22	5	
300-400	24	1	
400-500	14	1	
Over 500	2	0	
Total		85 (100%)	80 (100%)

Discrepancies in the totals are due to failure to obtain admission values in 4 patients, and discharge values in 9 patients, of this series.

The method of diastase determination used by the laboratory was that of Somogyi,[12] and consisted briefly in blood sugar determination before and after incubation of a blood sample with starch solution for 30 minutes. The difference between the two determinations is the diastase value, recorded as milligrams per 100 cc. of reducing substances. Normal values are stated by Somogyi[11] to fall within the limits of 60 and 180 mg. per 100 cc. Four per cent of normals

were found by Somogyi to fall below 60 mg., none above 180 mg. A limited number of determinations on normal controls at this hospital were within the limits of 60 and 180 mg. Somogyi stresses the normal constancy of an individual's diastase level, there being no tendency to physiologic fluctuation.

Results. The table lists the diastase values on admission and on discharge of the series of 89 cases of mumps. Three-fourths of the patients on admission were found to have abnormally high diastase levels. Three patients had subnormal levels on admission. On discharge, 20% were subnormal, and only 9% above normal.

In this series of 89 cases, there were 13 instances (15%) of pancreatitis, as indicated by symptomatology associated with a rise of the diastase value above the admission level. An examination of the admission diastase values of these 13 cases revealed that all but 1 were above normal, an incidence of 92% as compared with 73% for the series as a whole.

An attempt was made to correlate the degree of abdominal distention and that of pancreatic tenderness, as noted at the time of admission, with the diastase value on admission, but no statistically significant correlation was found. Neither did the 13 cases which subsequently developed pancreatitis exhibit these clinical findings on admission to any greater degree than the series as a whole.

Discussion. Diastase is known to be produced by the pancreas and by the salivary glands. In both instances, however, this production is released through excretory ducts and does not normally reach the blood stream. Injury to these glands does not decrease the blood diastase level, having in fact the opposite effect in pancreatitis[5,8,10] and possibly in salivary adentitis.[4] Hepatic impairment, however, causes a fall in blood diastase[7] and it is postulated, therefore,[3] that the diastase normally found in blood has its origin in the liver.

The number of subnormal diastase levels on recovery from mumps was surprisingly large, and is best accounted for by assuming some hepatic functional impairment.[1] In some cases of pancreatitis also, it was noted that the high diastase values fell to subnormal levels for a few days before returning to normal. Inasmuch as mumps is regarded as a generalized systemic disease[6,13] with a predilection for glandular tissues, it would not seem too far-fetched to suppose the existence of hepatic involvement in these cases. This is a possibility which could be investigated by use of additional liver function tests in following the course of mumps.

The high percentage of increased diastase values found on admission must indicate either an unexpected frequency of subclinical pancreatitis or a parenchymatous injury of the salivary glands. It is possible that both possibilities contribute to the rise in diastase. *A priori*, knowing that the salivary glands produce diastase, and that their histologic appearance is similar to that of the pancreas except for the absence of islands of Langerhans, it might be expected that the increased diastase of the blood is secondary to salivary gland injury, in a manner analogous to that which follows pancreatic injury. However, the fact that those cases which subsequently developed pancreatitis showed an even

greater percentage of increased diastase values on admission, would indicate either that these are the more severe cases of mumps, with greater salivary gland involvement, or that subclinical pancreatitis was already present and was accounting in part, at least, for the elevation in the blood diastase.

There appeared two ways in which this problem might be pursued. One was the method of Lagerlöf,[10] who has shown the diagnostic value in acute pancreatitis of diminished diastase content in the duodenal secretion of pancreatic juice following the injection of secretin. Though well established by Lagerlöf's careful and thorough work, this method of determining the presence or absence of pancreatitis was, unfortunately, not used by us because of the necessity of passing duodenal tubes routinely in our mumps patients. Instead, determinations of blood lipase were attempted, using the method of Cherry and Crandall.[2] This enzyme has been shown to be increased in the blood in pancreatitis,[2,9] but should not be affected in salivary adenitis since the salivary glands do not produce lipase.

After patient effort and careful control studies, however, the laboratory personnel and the author were convinced that quantitative blood lipase studies were not sufficiently reliable—at least in our hands. It is significant that Lagerlöf[10] has arrived at the same conclusion regarding the blood lipase determinations; this does not seem to be the opinion reflected in the American literature, however.

Summary. Blood diastase values were determined in a series of 89 cases of mumps on admission to hospital and on discharge. Seventy-three per cent were above normal on admission, and 9% on discharge. Three per cent were subnormal on admission, and 20% on discharge. Fifteen per cent of this series showed evidence of pancreatitis sometime during the course of illness.

Those cases which later developed pancreatitis had an especially high percentage of increased diastase values on admission. Studies intended to illuminate the possible rôle of the pancreatitis in producing these values did not prove feasible under our circumstances.

This study was under the supervision of Lt.-Col. Frederick Kellogg, Medical Service, who offered valuable suggestions. Laboratory work was supervised by Capt. Herman Bolker, Laboratory Service.

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OBSERVATIONS ON THE ORAL ADMINISTRATION OF CITRATED BLOOD IN MAN

III. The Effect on Temperature and the White Blood Cell Count*

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Fever is said to occur in 58 to 91% of patients with bleeding peptic ulcer.[1] It was present in 122 (84%) of 145 patients with bleeding peptic ulcer seen at the Cincinnati General Hospital between October 1, 1937 and March 30, 1943, who were free of complications known to be accompanied by fever. Fever was present in 100 (81%) of 123 additional "uncomplicated"† cases of hematemesis and melena due to ruptured esophageal varix, gastric carcinoma, gastritis, or undetermined cause. Pyrexia usually occurs within 24 hours after hematemesis or melena, lasts from a few days to a week or slightly longer, and may reach a maximum of 103° F. In cases of bleeding peptic ulcer it more frequently follows massive or moderately severe than mild hemorrhage.[1,3]

Perusal of the scant literature on this subject indicates that the cause of the fever is not known. According to Dill and Isenhour,[1] numerous factors have been invoked, including absorption of blood decomposition products, reduction in blood volume, anemia, associated gastritis, or increase in lability of the heat-regulating center as a result of asthenia or shock. According to these authors, the absorption of blood from the intestinal tract was assigned as the cause of the fever by Eichorst, Leichtenstern, Riegel, and Krehl. Hurst[2] stated in 1929 that "the old view that the pyrexia is due to the absorption of products of putrefaction of blood is generally correct."

As far as we are aware, the first attempt to evaluate experimentally the rôle of blood in the intestinal tract in the production of the fever was made by Dill and Isenhour.[1] They administered to 4 dogs, by stomach tube, approximately one-fourth the volume of each animal's blood. There was no effect on the temperature curves during the following 10 days. They also found that removing one-fourth of the dog's blood volume did not produce fever, nor did fever result from

* This study was aided by a grant from Parke, Davis & Company, through the coöperation of Dr. E. A. Sharp.

† Uncomplicated by a disease which could of itself produce fever.

the combined removal and introduction of this blood into the intestinal tract.

They introduced into the stomachs of 4 human subjects 500 to 600 cc. of citrated blood obtained by phlebotomy from patients with congestive heart failure and found no significant elevation of temperature during an ensuing 10-day period. They concluded that blood in the intestinal tract of man does not of itself cause a significant rise in temperature.

Experimental Observations. We thought it desirable to determine the effects of larger volumes of blood than used by these authors, since we believe that patients with hemorrhage from the upper digestive tract frequently lose a liter or more of blood. Accordingly, 6 patients were selected for study; 1 was 43 years old and the remainder between 53 and 60 years of age. Two had duodenal ulcer (1 with recent hemorrhage); 1, a jejunal ulcer; 2, chronic gastritis, and 1, polycythemia. The patient with the recent hemorrhage had had fever of 1 week's duration following his hemorrhage, with a maximum elevation of 101° F. He had a minimum red cell count of 1,500,000 and a count of 3,300,000 at the time he was given 1000 cc. of citrated blood. The patient with polycythemia received 800 cc. of his own blood removed by phlebotomy 3 hours before. Of the remaining 4 patients, 1 received 750 cc. of his own blood and 2 received 1000 cc.; 1 received 1850 cc. of citrated human blood obtained from the Blood Bank of the Cincinnati General Hospital.

The blood was given by stomach tube. In amounts up to 1000 cc. it was allowed to flow into the fasting stomach by gravity over a period of 30 to 60 minutes. The 1850 cc. of blood was divided into 3 portions given at 4-hour intervals. A hypodermic injection consisting of codeine sulfate gr. 1 and atropine sulfate gr. 1/150 preceded the administration of the blood in order to prevent too rapid passage through the intestinal tract. None of the subjects vomited the blood. The patients with peptic ulcer were on a Meulengracht or bland diet, while the others were on a regular diet during the period of this study.

Figure 1 is a record of the oral temperatures generally taken at 4-hour intervals for 48 hours preceding the administration of the blood and 72 hours following. A significant rise in temperature did not occur in any of the 6 subjects.

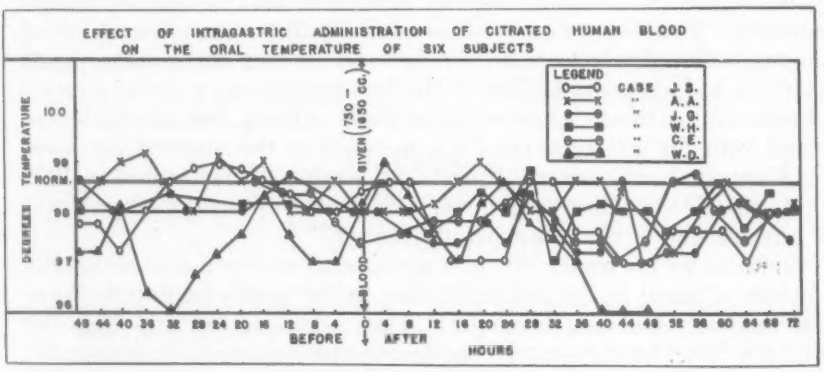

FIG. 1

Contrary to the experience of Dill and Isenhour,[1] leukocytosis has frequently followed hematemesis or melena due to various causes in patients admitted to the Cincinnati General Hospital, particularly in patients seen within 48 hours after the occurrence of hemorrhage. In 95 (65%) of 145 cases of "uncomplicated" bleeding peptic ulcer, the white cell count varied from 10,000 to

25,000, while a leukocytosis of 10,000 to 25,000 was present in 74 (60%) of 123 cases with hematemesis or melena due to ruptured esophageal varix, gastric carcinoma, gastritis, or undetermined cause.

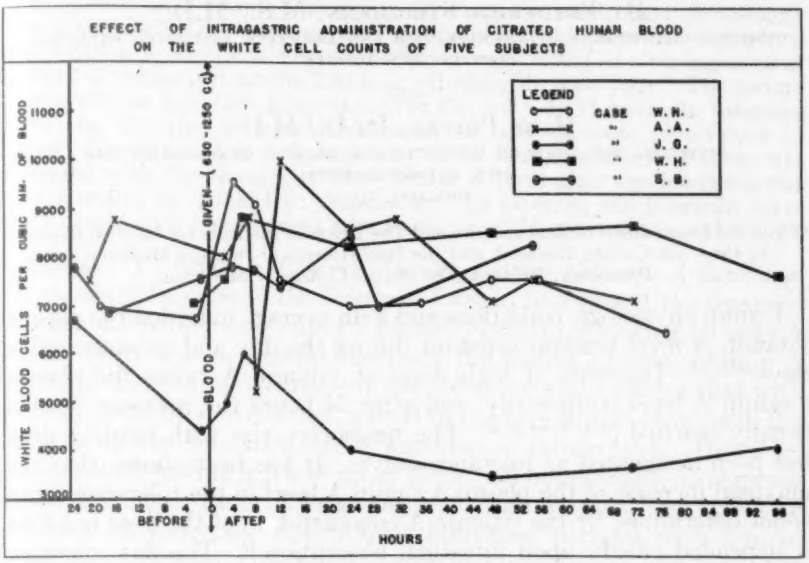

FIG. 2

The mechanism of the leukocytosis is presumably the same as that which follows hemorrhage in general. We were, nevertheless, interested to determine whether the presence of blood in the intestinal tract of itself had any influence on the leukocyte count. Accordingly, white blood cell counts were made at frequent intervals during the day preceding and at frequent intervals during the 72 to 96 hours following the intragastric administration of blood. No significant changes occurred (Fig. 2). Three of the subjects used in this study were the same as those used in the temperature study (2 with duodenal ulcer and 1 with chronic gastritis). The remaining 2 subjects were 33 and 37 years old; 1 was convalescing from pneumococcal pneumonia, while the other had recovered from a gastro-enteritis.

Summary. There was no significant elevation of temperature in 6 human male subjects within a 3-day period following the intragastric administration of 750 to 1850 cc. of citrated human blood. There was no significant change in the white blood cell count of 5 human male subjects in a 3- to 4-day period following the intragastric administration of 650 to 1250 cc. of blood.

Conclusion. The presence of citrated human blood in the intestinal tract of men does not produce fever or leukocytosis within a period of 3 to 4 days.

We wish to express our thanks to Dr. Paul Hoxworth, Director of the Red Cross Transfusion Service, for his coöperation in this study.

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THE INFLUENCE OF LARGE DOSES OF VITAMIN A UPON THE PLASMA VITAMIN A LEVEL*

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Under physiologic conditions and with average nutrition the plasma vitamin A level remains constant during the day and on consecutive days.[15,31,38] Ingestion of high doses of vitamin A raises the plasma vitamin A level temporarily, and after 24 hours the previous level is usually reached.[1,6,32,37,39,42,43] The temporary rise with ensuing drop has been designated as tolerance curve. It has been shown that the maximal increase of the plasma vitamin A level in the tolerance curve is not determined by the vitamin A concentration of the liver but that it depended chiefly upon intestinal absorption.[39] The flat tolerance curves found in liver diseases[6,39,42] were explained by impaired intestinal absorption due to liver damage.

Assuming that the tolerance curve mirrors the intestinal absorption of vitamin A, several problems arise which form the basis of this paper. (1) Is there a relation between the fasting plasma vitamin A level and the maximal response in the tolerance curve? (2) Is there a relation between the lipid content of the blood and the response in the tolerance curve? This question arises because Josephs[19,20,22] demonstrated in animals and children a relation between the response of the serum vitamin A level to the intake of high doses of vitamin A and the blood lipids as carriers of vitamin A. (3) Is there a difference in the response in the tolerance curve to equal amounts of esterified vitamin A or vitamin A alcohol or carotene? (4) Is there a more marked response in the tolerance curve when vitamin A is given orally or intramuscularly? (5) Does the simultaneous administration of vitamin E influence the tolerance curve? This question is raised because vitamin E as an antioxidant may reduce the destruction of vitamin A in the intestinal lumen and thus increase its absorption.[2,11,18]

Material and Method. Hospital patients suffering from various diseases were studied. Each subject received 75,000 I.U. of vitamin A ester† in 2 cc. oil mixed in fruit juice. The plasma vitamin A level was determined before, and 3, 6, and 24 hours after administration of vitamin A. The Carr-Price

* Supported by a grant from the Scientific Committee of the American Medical Association and from the S. M. A. Corporation, Chicago.

† Distilled vitamin A concentrate (natural ester form, distilled from fish liver and vegetable oil) containing 200,000 U.S.P. XI units per gram, generously supplied by Distillation Products, Inc., Rochester, N. Y.

reaction was used for determination following the method of Kimble.[24] The measurements were made either by the Sheard-Sanford photoelectric colorimeter or by the copper sulphate standard according to the method of Josephs.[19] The details of the procedure were described in a previous publication.[40] In 20 cases, the total plasma fat[5] and in 88 cases the total blood cholesterol[25] were determined. Furthermore, in 7 cases the first tolerance curve obtained after vitamin A esters was compared with a second obtained after ingestion of 75,000 I.U. vitamin A alcohol* in 2 cc. oil mixed in fruit juice. The second tolerance curve was made a few days after the first. In 11 cases, the tolerance curve was repeated after administration of beta carotene, equivalent to 75,000 I.U. vitamin A in 2 cc. corn oil. In 14 cases, the tolerance curve was compared with the changes of the vitamin A level after the intramuscular administration of 75,000 I.U. vitamin A.† In 13 cases, the tolerance curve was repeated with simultaneous administration of 50 mg. alpha-tocopherol.‡

Results. I. *Relation Between Fasting Plasma Vitamin A Level and the Maximal Increase in the Tolerance Curve.* In Figure 1 the maximal increase in the tolerance curve is plotted against the fasting vitamin A level. There was no relation between the fasting plasma vitamin A level and the maximal increase in the tolerance curve except that with a fasting level of above 50 μg., a level in the high ranges of normal, the response in the tolerance curve was always satisfactory. However, patients with fasting levels of up to 40 μg. had occasionally no response or almost none. Liver damage (as evidenced by jaundice) exerts an influence on intestinal absorption. Jaundiced patients with zero or nearly zero plasma vitamin A levels had usually no response, but sometimes the maximal increase was quite marked. If the jaundice cases are grouped according to duration of liver damage, it is evident that in patients with acute liver damage, as in acute hepatitis or in secondary hepatitis of obstructive jaundice, no or very slight response was found; whereas in patients with chronic liver damage, as in cirrhosis, sometimes a satisfactory response in the tolerance curve was observed.

II. *Relation Between the Maximal Increase in the Tolerance Curve and the Concentration of Fat and Cholesterol in the Blood.* The blood lipids are usually considered the carriers of vitamin A. The possibility thus arises that the amount of available carrier substances may influence the response in the tolerance curve. However, a comparison between the total blood lipids and the maximal increase of the plasma vitamin A level following the vitamin A administration reveals no relation (Fig. 2.) High maximal increases were found with both high and low blood lipids. The lipids themselves did not rise after administration of vitamin A. The maximal increase of the plasma vitamin A level after administration of vitamin A plotted against the total cholesterol in the blood (Fig. 3) shows no consistent relation. In fact, high cholesterol levels were frequently associated with a lack of response in the tolerance curve. This observation, however, was made mostly in patients with obstructive jaundice due to a malignant condition of the

* Furnished as vitamin A alcohol concentrate containing 600,000 units.

† Kindly supplied in ampules containing 100,000 U. per cc. by E. R. Squibb & Son, New Brunswick, N. J.

‡ Courtesy of Distillation Products, Inc., Rochester, N. Y.

head of the pancreas or common duct. Similar to the total lipid content, the total cholesterol also failed to rise following the administration of 75,000 I.U. vitamin A.

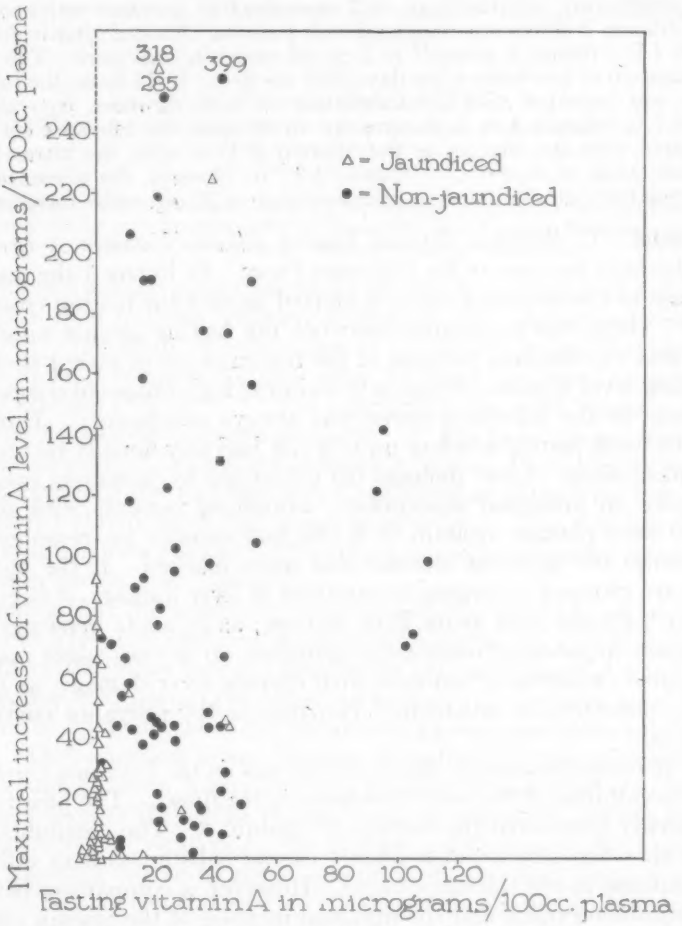

FIG. 1.—Fasting vitamin A level and the maximal increase of the plasma vitamin A level after the administration of 75,000 I.U. vitamin A.

III. *Influence of Type of Vitamin A Administered.* *A.* Tolerance Curves After Administration of Vitamin A alcohol: In 7 patients, 3 without and 4 with jaundice, the vitamin A tolerance curve after ingestion of the usual 75,000 I.U. vitamin A ester was compared with the tolerance curve obtained after administration of 75,000 I.U. vitamin A alcohol. Only a slight difference in the maximal increase in the two tolerance curves was noted.

B. Tolerance Curves After Carotene Administration: In 11 patients (6 with jaundice) the vitamin A tolerance curve after ingestion of 75,000 I.U. vitamin A was compared with the change of the plasma

vitamin A level after ingestion of beta-carotene equivalent to 75,000 I.U. vitamin A. The vitamin A level did not rise appreciably after the carotene intake, although normal vitamin A tolerance curves were obtained in some cases (Fig. 4). The plasma carotenoid level itself was slightly elevated after carotene administration, whereas vitamin A ingestion changed only occasionally the carotenoid level.[6]

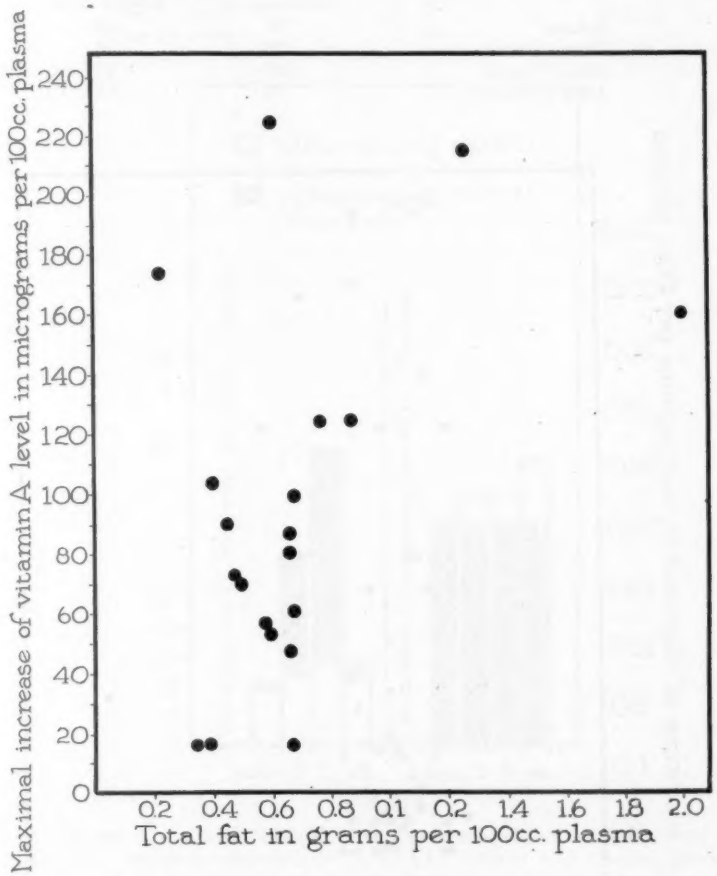

FIG. 2.—Total fat in the plasma and the maximal increase of the plasma vitamin A level after the administration of 75,000 I.U. vitamin A.

IV. *Influence of Route of Administration.* In 14 cases (hospital controls and patients with various diseases, including liver disease) the tolerance curves after the oral intake of 75,000 I.U. of vitamin A were compared with those made after intramuscular injection of 75,000 I.U. vitamin A. No response in the tolerance curve (Table 1) after intramuscular injection of vitamin A was noted; the average maximal rise being only 4 μg., in contrast to the usual response following the oral intake of the same dose of vitamin A. In only 2 cases was the plasma vitamin A level higher 24 hours after the intramuscular administration

than prior to it; whereas in the other 12 cases, the curve had returned to the original level.

TABLE 1.—AVERAGE PLASMA VITAMIN A LEVEL IN 14 CASES, BEFORE AND AFTER ORAL AND INTRAMUSCULAR ADMINISTRATION OF 75,000 I.U. VITAMIN A

	Plasma vitamin A level in micrograms per 100 cc.	
	Oral administration	Intramuscular administration
Before	37	44
After 3 hours	138	48
After 6 hours	200	48
After 24 hours	62	45

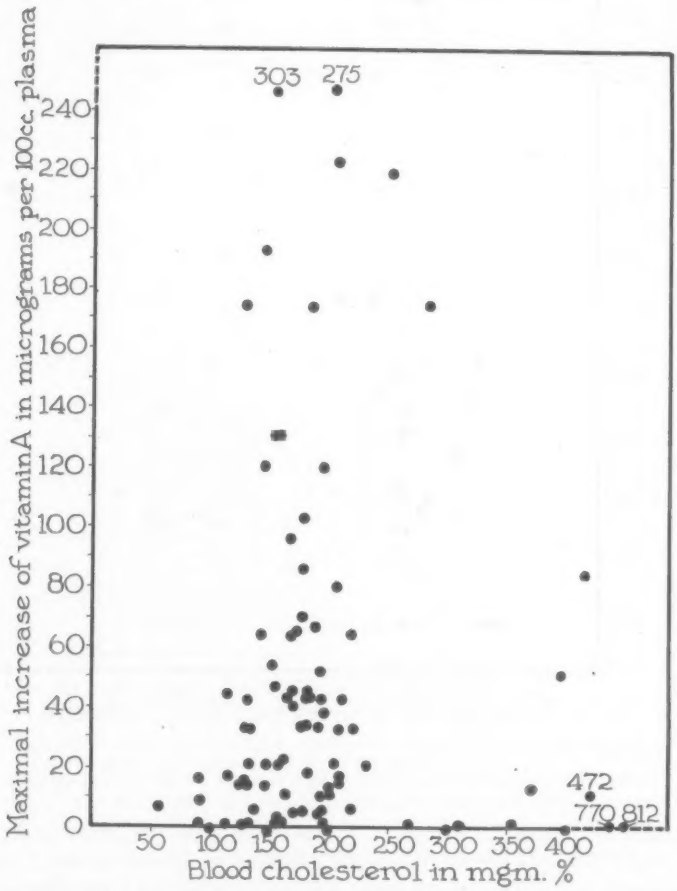

FIG. 3.—Total blood cholesterol and the maximal increase of the plasma vitamin A level after the administration of 75,000 I.U. vitamin A.

V. *Influence of Vitamin E on the Tolerance Curve.* When the vitamin A tolerance curves were repeated with the simultaneous administration of 50 mg. alpha-tocopherol some variations of the tolerance curve in both directions were noted. The averages of the two tolerance curves, however, were similar (Table 2).

TABLE 2.—AVERAGE PLASMA VITAMIN A LEVEL IN 13 CASES, BEFORE AND AFTER INGESTION OF 75,000 I.U. VITAMIN A WITH AND WITHOUT SIMULTANEOUS ADMINISTRATION OF 50 MG. ALPHA-TOCOPHEROL

	Plasma vitamin A level in micrograms per 100 cc.	
	Without alpha-tocopherol	With alpha-tocopherol
Before	26	33
After 3 hours	68	80
After 6 hours	87	90
After 24 hours	36	39

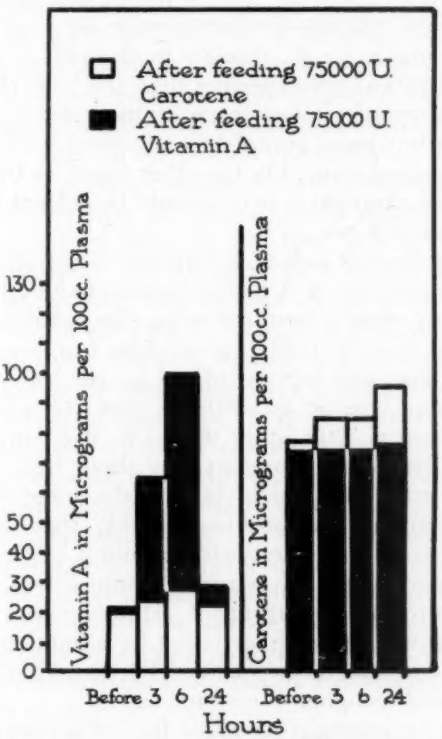

FIG. 4.—Averages of plasma vitamin A and carotene levels before, 3, 6 and 24 hours after ingestion of carotene equivalent to 75,000 I.U. vitamin A in 11 cases (white columns), compared to the averages of the tolerance curves following the ingestion of 75,000 I.U. vitamin A (white plus black columns).

Discussion. It might be anticipated that the response of the plasma vitamin A level to the intake of high doses of vitamin A should run parallel to the height of the initial plasma vitamin A level, since both plasma vitamin A level and tolerance curve evidently depend upon the intestinal absorption of vitamin A. The influence of the nutritional intake of vitamin A upon the plasma level is well established,[21,23,28,29,33,48] and the relation between intestinal absorption and tolerance curve has recently been emphasized.[6,37] Our findings, however, show that the plasma level and the maximal increase in the tolerance curve are parallel only when the former is high.

The usual lack of parallelism between the plasma vitamin A level and the maximal increase in the tolerance curves may be partly explained by the fact that the plasma vitamin A level depends not only upon the intestinal absorption but also on the ability of the liver to regulate the blood vitamin A level.[1,36,38] Thus, in healthy individuals the plasma vitamin A level may be maintained for some time even if no vitamin A is taken,[7,35,45] while in patients with acute liver damage the plasma vitamin A level drops quickly despite a sufficient intake of vitamin A.[8,30,34,38]

Another explanation for the lack of parallelism between the plasma vitamin A level and the rise of the tolerance curve are abrupt changes in intestinal absorption, *i. e.*, changes in absorption will influence the shape of the tolerance curve speedier than the level of the plasma vitamin A. Thus, in the initial stage of liver damage, the intestinal absorption may be almost completely inhibited while the blood level has not quite reached zero. On the other hand, in the recovery stage from liver disease, absorption may already be normal while the plasma vitamin A level is still low.

A third factor for this lack of parallelism is variations in the oxidative destruction of vitamin A in the lumen of the intestine. Various experiments have shown that following the administration of high doses of vitamin A, only a small percentage can be accounted for.[4,27] If we consider a maximal increase of 100 μg. per 100 cc. as normal and assume the plasma volume as 3000 cc., then the accounted-for vitamin A in the blood is 3000 μg. or 9840 I.U. if a conversion factor of 3.28 is used.[19] This would represent only about 13.3% of the ingested vitamin A. A certain amount is doubtlessly stored in the liver since the amount determined in the blood is only that found during the transport. However, a destruction of vitamin A by oxidative processes should also be considered. Recently, vitamin E was considered to be an important antioxidative agent.[5,18] However, our attempt to increase the height of the tolerance curve by administration of 50 mg. of alpha-tocopherol was unsuccessful. Further attempts with variations in the dose of tocopherol seem indicated.

In the search for causes responsible for variations in the tolerance curve, the total lipid concentration of the blood was discarded as a factor. Similarly the blood cholesterol level does not seem to have any relation to the height of the tolerance curve.

However, the form in which the vitamin A is administered is of importance. Thus, if it is given in the form of the provitamin beta-carotene, the plasma vitamin A and carotenoid level hardly change. The low response in the tolerance curve coincides[9,12,35,46] with some human[4,8,12,27] and animal[10,41] experiments. The question may arise whether this difference is due to destruction of carotene in the intestine, inability of the intestine to absorb carotene, or immediate liver storage of the carotene before the blood level rises. The fact that, of enormous doses of carotene a much smaller part is probably absorbed than of similar doses of vitamin A, does not necessarily imply that the same

difference prevails after intake of the much smaller doses of carotene contained in the food.

However, whether the vitamin A is taken as an alcohol or in the esterified form does not influence the shape of the tolerance curve, which observation agrees with experiments on rats.[14,16] This finding is significant, since vitamin A is absorbed as alcohol and esters are split during absorption.[17] Difficulties in the vitamin A esters hydrolysis are not an important factor in the shape of the tolerance curve.

The route by which vitamin A is administered plays a part in the shape of the tolerance curve.

The question of parenteral supply of vitamin A is important in view of the fact that many patients, especially in liver disease, are almost unable to absorb vitamin A administered orally.[6,39,42] However, following the intramuscular injection of 75,000 I.U. vitamin A, we did not observe a rise in the plasma vitamin A level. The fact that the slight rise in the plasma vitamin A level encountered in few cases usually disappeared within 24 hours, speaks against the possibility that delayed absorption accounts for this lack of response in the tolerance curve. Rourke and Stewart[44] gave intramuscular injections of 500,000 I.U. to patients with obstructive jaundice. They likewise failed to note a rise in the plasma vitamin A level, but in subsequent biopsies found relatively higher liver stores in these than in untreated cases. This would imply that, despite a lacking rise of the plasma vitamin A level, the liver stores of vitamin A are increased. However, in view of the impaired release of vitamin A from the liver in hepatic diseases[34,40] the intramuscular administration of vitamin A is of doubtful value since, apparently, only the vitamin A which circulates in the plasma is of functional significance. The relative ineffectiveness of the intramuscular injection of vitamin A in oil, as compared to the oral intake which was also found in various animal and human experiments,[3,13,25,41,47] may be due to the vehicle used. The injection of vitamin A to animals in aqueous colloidal preparations[26] or propylene glycol[3] results in improvement of vitamin A deficiency signs as well as in increased liver stores.

Summary. This study deals with several factors which may influence the response of the plasma vitamin A level to the ingestion of high doses of vitamin A (tolerance curve).

1. The shape of the tolerance curve is not necessarily related to the fasting plasma vitamin A level. This indicates that the plasma vitamin A level depends not solely upon current efficiency of the intestinal absorption for vitamin A.

2. The administration of the antioxidant vitamin E (in the given amount) did not influence the tolerance curve.

3. No apparent relation was found between the fat and cholesterol concentration in the blood and vitamin A tolerance curve.

4. Ingestion of vitamin A alcohol or vitamin A esters causes a similar rise of the plasma vitamin A level in the tolerance curve, whereas doses of carotene only have a minimal effect.

5. Intramuscularly administered vitamin A does not appreciably raise the plasma vitamin A level.

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A METHOD FOR STANDARDIZING PENICILLIN

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The use of penicillin in the treatment of infections is accompanied by a number of technical problems not common to other therapeutic agents. One of the difficulties results from the tendency for the potency of penicillin to decrease under a variety of conditions. At the present stage of development of production of penicillin there is often a wide discrepancy between the estimated strength of a product at the time it is prepared and the actual strength at the time of use. This is not surprising in view of the great lability of penicillin. In some instances these differences appear to be due to the method of assay employed. Because of the scarcity of penicillin and the difficulties involved in its manufacture, it is important not to use more of it in the treatment of individual patients than is necessary; likewise it is most important to use enough. It is desirable, therefore, to be able to determine the strength of a preparation of penicillin at the time it is being administered.

One of the standard methods for assay of penicillin is that described by Abraham and co-workers.[1] It is known as the Oxford method and the Oxford unit is generally used to express the potency of a preparation even when it has been standardized by methods other than the Oxford method. Broth dilution methods employing serial dilutions of penicillin may be used for rough determinations of potency, but because the differences between concentrations are twofold, the error is necessarily great. In the turbidimetric method of Foster[2] the differences between concentrations of penicillin used are relatively small, and the accuracy of the method is said to be within ±10 or 15%. Foster and Woodruff[3] have recently compared other methods of assay with the turbidimetric method.

Methods sufficiently sensitive for this purpose require the use of a preparation of penicillin of known potency as a standard in individual tests. One of the chief hazards in the assay of penicillin is the maintenance of a suitable standard. Under ordinary conditions the standard must be compared with other standards from time to time to be sure that it has not decreased in potency.

A method in use in this laboratory has been found reliable when compared with other methods; furthermore it does not require the use of a reference standard in individual tests. A determination is made of the amount of penicillin that will prevent the growth of a strain of *Diplococcus pneumoniæ* in semisolid tissue culture medium. The method is an adaptation of one described by King, Henschel and Green in their studies on sulfonamide compounds.[9,10] It has been used in comparative studies on the bacteriostatic activity of antibacterial agents of microbial origin and germicides.[4,6] The pneumococcus was chosen as a test organism because it grows well in the

medium employed, it is sensitive to the action of penicillin and it does not liquefy the plasma clot, thus making possible an accurate colony count throughout the incubation period.

Experimental. The general laboratory procedures followed were similar to those described by King for tissue culture technique.[7]

Tissue Culture Medium. Healthy adult male rabbits were used exclusively as a source of blood for the preparation of medium. Rabbits were not fed during the 24 hour period before they were used. Blood was obtained under sterile conditions by cardiac puncture or by carotid cannulation with the animal under light ether anesthesia. Serum was prepared and heparin was added to a portion of the blood for the preparation of plasma. The solution of heparin used contained 0.04% of purified heparin (Connaught Laboratories) and 0.8% of sodium chloride. This solution was sterilized by Berkefeld filtration and 0.25 cc. was used for 15 cc. of blood. Tubes containing blood to which heparin had been added were thoroughly chilled before being placed in the centrifuge. After the blood had been centrifuged the plasma was transferred to a sterile tube and packed in ice. Serum and plasma showing abnormal cloudiness or opalescence, or a considerable degree of hemolysis, were discarded. A slight degree of hemolysis did not appear to affect the results. A serum-chick embryo extract was prepared by extracting chick embryos of 8 days of incubation with rabbit's serum in the proportion of 1 embryo to 5 cc. of serum.

Bacterial Cultures. A strain of *Diplococcus pneumoniæ* Type 7 originally isolated from exudate from an empyema cavity was used as the test organism. Cultures were grown in Hartley broth containing approximately 10% of horse serum. When a culture had attained maximal growth, suitable dilutions were made in Hartley broth and added to the serum-chick embryo extract in the proportion of 1 part of the bacterial suspension to 40 parts of serum extract. The final concentration of the original bacterial culture in the tissue culture clot was approximately 1:10,000,000. This inoculum usually resulted in the appearance of 20 or more bacterial colonies in each preparation. It was found that a more uniform bacterial count could be obtained on different days by using a suspension of pneumococci stored in divided amounts in solid carbon dioxide than when freshly grown cultures were used. Tubes containing tissue extract to which pneumococci had been added, as well as tubes containing plasma, were kept chilled throughout the experiment. It was found to be important to use freshly prepared extract for each day's determinations. Some variation resulted when plasma and extract that had been prepared the day before were used.

Penicillin. The penicillin used to standardize the method was a preparation of the sodium salt of penicillin obtained from the Northern Regional Research Laboratories of the United States Department of Agriculture through the courtesy of Dr. Robert Coghill. By recent comparison with other standards by means of the Oxford method its potency had been determined as 28 Oxford units per mg. Additional tests were carried out with a standardized preparation of the calcium salt of penicillin obtained through the courtesy of Dr. Coghill. The potency of this preparation was 135 Oxford units per mg. Twelve other preparations from 5 different sources were tested (Tables 1 and 2). As soon as they were received, individual samples were weighed under sterile conditions and added to 0.8% solution of sodium chloride to make a concentration of 1:500. These stock solutions were stored in divided amounts in solid carbon dioxide until they were needed for the preparation of suitable dilutions in 0.8% solution of sodium chloride at the time the tests were made. Experiments with 1 sample of penicillin were usually carried out within a period of a few weeks, as prolonged storage of the stock solutions in solid carbon dioxide sometimes resulted in a loss of potency.

In instances in which the potency of penicillin received was expressed as the number of Oxford units per ampule and the total weight of the sample was not

TABLE 1.—ASSAY OF PENICILLIN

Source of penicillin	Sample No.	Test No.	Colonies per culture (controls)	Concentration of penicillin: Causing total inhibition (μg./cc.)	Concentration of penicillin: Not causing total inhibition (μg/cc.)	Assay at source (Oxford units/mg.)	Assay, present method (Oxford units/mg.)	Reassay at source (Oxford units/mg.)
A	1	1	60	1.00	0.50	98	84	
		2	100	1.00	0.90			
B	1	1	20	0.50	0.25	357	168	125
		2	36	0.50	0.40			
		3	15	0.50	0.40			
	2	1	20	0.50	0.25	138	210	
		2	12	0.40	0.30			
		3	36	0.40	0.30			
		4	22	0.40	0.30			
	3	1	21	1.00	0.50	182	140	
		2	24	1.00	0.50			
		3	15	0.60	0.50			
	4	1	60	0.32	0.16	200	262	
		2	16	0.32	0.16			
	5	1	26	0.41	0.40	215		
		2	25	0.43	0.41	..	205	
		3	32	0.41	0.40			
		4	20	0.40	0.36			
C	1	1	24	0.66	0.50	250	142	146
		2	28	0.62	0.59*			
		3	26	0.59	0.56			
		4	32	0.59	0.56			
		5	150	0.59	0.56			

* One colony only in all 4 cultures at this dilution.

TABLE 2.—ASSAY OF PENICILLIN IN TERMS OF OXFORD UNITS PER AMPULE

Source of penicillin	Sample No.	Test No.	Colonies per culture (controls)	Concentration of penicillin: Causing total inhibition (Oxford units/cc.*)	Concentration of penicillin: Not causing total inhibition (Oxford units/cc.)	Assay at source (Oxford units per ampule)	Assay, present method (Oxford units per ampule)	Reassay at source (Oxford units per ampule)
B	6	1	42	0.080	0.060	10,000	10,500	
	7	1	150	0.080	0.060	10,000	10,500	
		2	42	0.080	0.060			
C	2	1	22	0.107	0.094	30,000	23,550	21,000
		2	24	0.107	0.094			
		3	28	0.107	0.094			
D	1	1	25	0.100	0.084	10,000	8,400	
		2	32	0.100	0.084			
E	1	1	32	0.250	0.166	25,000	8,400	
		2	20	0.250	0.166			

* Values are expressed in terms of original assay at the source. The end-point in this method is 0.084 Oxford units per cc.

known, the results of tests were expressed in terms of Oxford units per ampule instead of Oxford units per mg. (Table 2). The results of the individual tests were expressed in terms of the potency as determined at the source, and the final estimation of the value of the product was arrived at by multiplying the number of Oxford units per ampule as determined at the source by the fraction $\frac{0.084}{\text{Oxford units necessary to inhibit}}$.

Plasma Clot Cultures. Portions of each dilution of penicillin to be tested were added to both plasma and serum-chick embryo extract at the time the

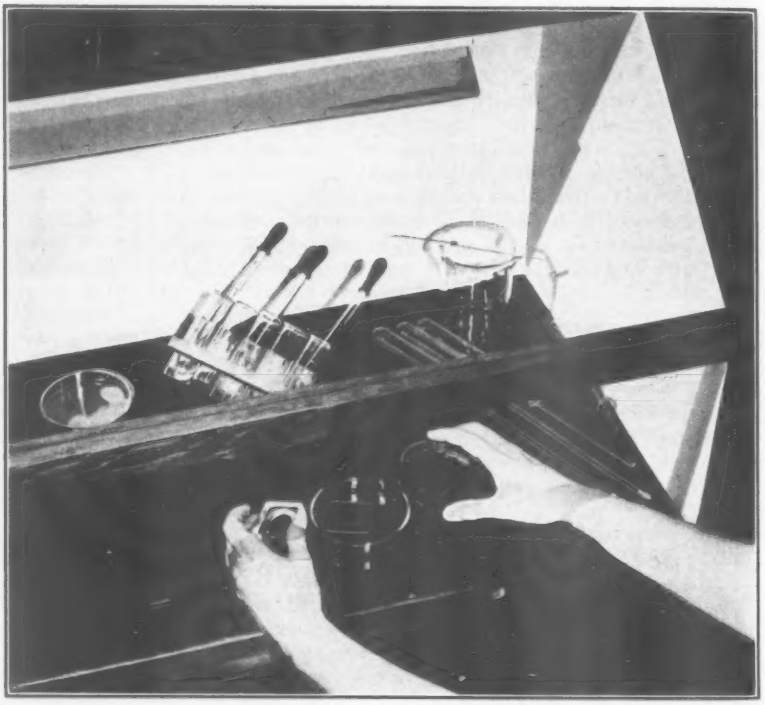

FIG. 1.—Preparation of cultures for the assay of penicillin. The photograph shows the arrangement of equipment in the culture hood. This view shows a plasma clot culture in a Petri dish just before it is to be sealed with a hollow ground slide. The other Petri dish contains sterile 22 mm. round coverslips. Tubes held at an angle of 45° in the rack are used for the following purposes: the first tube, from left to right, contains saline solution used to attach 22 mm. round coverslips to heavier square glass slides; the second tube is used to receive discarded mixtures of plasma and penicillin prepared in the third tube; the fourth tube is used to receive discarded mixtures of serum extract containing pneumococci and penicillin which had been mixed in the fifth tube for the preparation of cultures. Two pipets of 1 cc. capacity and one pipet of 0.2 cc. capacity used for measuring plasma, serum extract and solutions of penicillin respectively are shown with tips resting in sterile tubes.

cultures were made in order to insure a uniform concentration of penicillin throughout each culture. Since the amount of medium necessary for each group of cultures was small, 0.1 cc. portions of solution of penicillin were added to 0.9 cc. of plasma and serum extract respectively. Control cultures received a tenth by volume of 0.8% solution of sodium chloride instead of penicillin. The same mixing tubes and standardized pipets could be used for testing various concentrations of the same sample of penicillin by preparing cultures containing the least amount of penicillin first. Serum and plasma were

removed carefully from the mixing tubes after one group of cultures had been made and before medium was prepared containing a greater amount of penicillin.

The preparation used in making the culture was a modified Maximow type of preparation in which the culture was planted on a 22 mm. round coverslip attached by a small drop of saline solution to a heavier glass slide. With a standardized pipet 1 drop (approximately 0.05 cc.) of plasma containing penicillin was placed on the coverslip and evenly distributed by means of a sterile wire. Three drops of serum extract containing the test organism and penicillin were added to the drop of plasma on the coverslip and well mixed. Four cultures were prepared for each experimental condition. Each culture was covered with a sterile, hollow ground slide rimmed with petrolatum (Fig. 1). At the conclusion of the experiment cultures were sealed with a mixture of paraffin and petrolatum and were incubated at 37° C. in a specially constructed down-draft incubator.[8] Final observations were made after approximately 36 hours of incubation. At that time the number of bacterial colonies in each culture was determined with the aid of a dissection microscope at a magnification of 7×. An estimate was made of the average number of colonies present in control cultures not containing penicillin. An end-point was chosen arbitrarily as the lowest concentration of penicillin that would completely prevent the appearance of bacterial colonies in all 4 cultures. This end-point was determined several times for each preparation if the size of the sample would permit. The initial test in each instance was usually done with concentrations of penicillin spaced more widely apart than in subsequent tests in order to determine the range of activity of the sample. Several different preparations were tested on the same day.

Results. It was found that the growth of the test organism was prevented by 3μg. per cc. of the standard sodium salt of penicillin but not by 2.86 μg. per cc. Since the potency of this standard was 28 Oxford units per mg. the amount of penicillin necessary to prevent bacterial growth was presumably 0.084 Oxford units per cc. in the final tissue culture clot. Using this value the potency of each of the other preparations was determined by dividing 84 by the number of micrograms of each sample necessary to cause total inhibition. In tests done with a second standard, a calcium salt of penicillin, 0.59 μg. per cc. caused total inhibition of bacterial growth; thus the potency as determined by this method was 142 Oxford units per mg. This result showed an agreement of within 5% with the original assay of potency of 135 Oxford units per mg.

The results of individual tests with preparations of penicillin from different sources appear in Tables 1 and 2. Similar results were usually obtained on different days with the same sample of penicillin, particularly when widely spaced concentrations of the drug were used as in earlier tests. When there were smaller differences between concentrations used, as in the case of sample B5, varied results were obtained; however, the variation in this instance was within a range of 10%.

The difference between the results of assay of a product at the source and the value determined by this method was sometimes very great. All samples showing a greater potency by the present method than that claimed by the manufacturer were obtained from one source. In the case of 2 samples from source C the material was tested again at the source by the Oxford method and the results showed good agreement with the results obtained in this laboratory. Results of tests on

preparations A and D did not differ more than 16% from the results obtained at the source. Sample E was apparently less than half as potent as the estimate at the source would indicate.

Comment. The disadvantages of the method described here are those common to tissue culture technique in general, and no attempt will be made to minimize the difficulties to be overcome where tissue culture facilities are not already available. The method does offer certain unique advantages not only for the assay of penicillin but also for quantitative studies on other antibacterial agents. Experience with the use of the tissue culture preparation in bactericidal tests over a period has resulted in the conclusion that certain Gram-positive cocci grow with remarkable regularity when cultivated under these conditions. Tissue culture mediums prepared in a similar fashion appear to be more uniform than the usual bacteriologic mediums. The same concentration of penicillin tested at different times regularly caused the same degree of inhibition of bacterial growth. Relatively small amounts of penicillin are sufficient for the performance of a number of tests. Antibacterial agents less diffusible than penicillin may also be studied and compared by this technique.

This method is not recommended for determining the amount of penicillin in a patient's blood during treatment, as the presence of human serum in cultures decreases the accuracy of the results. Fortunately it is not necessary to know the concentration of penicillin in the blood in order to obtain good therapeutic results. It has been found that when adequate amounts of penicillin are given by almost continuous intravenous administration good results may be obtained in spite of the fact that penicillin cannot be detected in the blood by broth dilution methods.[5] It is much more important to know how much penicillin the person under treatment is receiving than to be able to detect the presence of penicillin in the blood by methods available at the present time.

Summary. A method has been described for the standardization of penicillin in which a determination is made of the amount of penicillin necessary to prevent the growth of pneumococci in semisolid tissue culture medium.

The principal advantage of this method is that it is not necessary to use a standard preparation of penicillin in the performance of the test. The amount of penicillin needed for a determination of potency is small. The accuracy of the method appears to compare favorably with that of the Oxford method in a limited number of tests. Repeated tests with the same sample of penicillin indicate that the variation of the results obtained is fairly small.

Preparations of penicillin from different sources have been standardized by this method. Results obtained as well as tests done elsewhere indicate that the actual potency of a product may be significantly different from the estimated potency at the time of preparation.

I wish to thank Dr. Wallace E. Herrell, Division of Medicine, Mayo Clinic, for valuable assistance with this study.

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SULFANILAMIDE AS A PROPHYLACTIC MEASURE IN RECURRENT RHEUMATIC INFECTION

A Controlled Study Involving 131 "Patient-Seasons"

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Previous reports suggest that sulfanilamide is of value as a prophylactic agent against recurrences of rheumatic fever. In August, 1942, Thomas[4] summarized the work of a number of clinics in the use of small, daily doses of sulfanilamide. In that series, the recurrence rate was less than 1% among several hundred treated patients. Since then, Hansen, Platou and Dwan[2] have reported similarly favorable results.

Because of the vagaries of rheumatic fever, the experience of any one clinic may be distorted. Geographic differences must be evaluated, and it is important, therefore, to consider results from many different regions. The present report, which confirms the observations of other investigators, should be appraised, not alone, but as an addition to the accumulated data. Toxic manifestations were not severe, and they will be discussed in detail.

Method. A program of prophylaxis was undertaken among out-patients of the Cardiac Clinic of Milwaukee Children's Hospital during two seasons (1941–42 and 1942–43). The method of control was designed to insure random selection as far as possible. Patients had previously been assigned in rotation to a clinic held on Monday, Wednesday or Saturday, and in most instances they had visited the same clinic for months or years. Children with a history of definite rheumatic fever or chorea and those with undoubted rheumatic heart disease, even though there was no positive history, were included in the study. All such patients in the Monday or Saturday clinics received sulfanilamide, and those in the Wednesday clinic acted as controls. In every instance, the rheumatic process was regarded as quiescent when the study began.

The season extended from October or November to May or June. The period of observation averaged 5.5 months each season for patients in the control group and 6.3 months for those who received sulfanilamide. Some

children dropped out of both groups before they had been in the study as long as 4 months, and they have not been counted in this report. None of those who discontinued the study developed recurrences while under observation. Patients receiving sulfanilamide came to the clinic every 3 or 4 weeks, and those in the control group appeared at slightly longer intervals. In addition to history and physical examination, the erythrocyte sedimentation rate, leukocyte count, hemoglobin and throat culture were obtained at each visit. The blood sulfanilamide level was determined in those who were receiving the drug. Electrocardiograms, Roentgen rays, and other laboratory work were requested when indicated.

There were 32 children in the control series, and some were in this group both years, so that, altogether, 42 "patient-seasons" are represented. The treated group consisted of 69 patients comprising a total of 89 patient-seasons during the 2 years. Among those who received no medication, there were 15 boys and 17 girls; the range of age was 4 to 14 (average, 8.6 years). There were 39 boys and 30 girls in the treated group; the ages ranged from 4 to 15 (average, 9.5 years).

Most patients were given 15 gr. (1 gm.) of sulfanilamide daily in three divided doses. At times, as much as 30 gr. (2 gm.) or as little as 5 gr. (0.3 gm.) daily were used, depending on the blood sulfanilamide level and the presence of toxic symptoms. An attempt was made to maintain the level between 1 and 3 mg. per 100 cc., but it ranged from 0 to 6.6 mg.

Results. *Rheumatic Recurrences.* During the two seasons, none of the treated children developed a recurrence of rheumatic fever. Thomas *et al.*[5] have appropriately defined a major rheumatic episode as an illness lasting at least a week, in which fever, polyarthritis, active carditis, chorea, or other signs are unequivocal. A minor rheumatic episode is characterized by transiently painful, swollen joints, or mild choreiform movements. There were 3 (7.2%) major and minor rheumatic episodes among the 42 control patient-seasons (Table 1).

The one major recurrence affected a girl of 14, who had suffered two previous recrudescences following her first attack of rheumatic fever in 1935. She had well-established mitral insufficiency. She was discharged from the Convalescent Home in June, 1941 and entered the control group in October, 1941. The first season she enjoyed unusually good health, and she was well at the start of the second season. A sore throat late in December, 1942 was accompanied by fever and pain in both knees for several days. Although she was not seen until 2 weeks after this episode, it was regarded as recurrent rheumatic fever. She was kept in bed from January to April, 1943, and during this time tachycardia, anemia, failure to gain weight, and persistent elevation of the sedimentation rate were observed.

Both minor recurrences developed during the first season. One affected a girl of 6, who had mitral insufficiency but no definite rheumatic history. In December, 1941, and January, 1942, she showed choreiform movements and an elevation of the sedimentation rate. These signs were absent the remainder of the year and the following season.

The other patient was a boy of 8, who had mitral insufficiency without a definite history. In January, April and May of 1942, he complained of nervousness and was observed to manifest definite choreiform movements.

Thomas *et al.*[5] have classified a questionable rheumatic episode as any illness in which the diagnosis of rheumatic fever is in doubt as well as such symptoms as epistaxis, sore throat, arthralgia, or precordial pain. Among control patient-seasons, 13 (31%) experienced 23 questionable episodes. Of the children treated, 19 (21.4%) presented 23 such incidents (Table 1).

TABLE 1.—RESULTS OF SULFANILAMIDE PROPHYLAXIS

	42 control patient-seasons		89 treated patient-seasons	
	No.	%	No.	%
Major rheumatic episodes	1	2.4	0	0
Minor rheumatic episodes	2	4.8	0	0
Questionable rheumatic episodes	13	31.0	19	21.4
Total	16	38.2	19	21.4
Initially positive beta hemolytic streptococcus throat cultures	17	40.4	41	46.1
Subsequent throat cultures	157	..	546	
Subsequent positive throat cultures	76	48.4	223	40.8

Throat Cultures. Comparative results are shown in Table 1. At the start of each season, 17 (40.4%) of the control patients and 41 (46.1%) of the children who were to receive sulfanilamide showed positive throat cultures for the beta hemolytic streptococcus. Among the untreated subjects, 157 subsequent cultures were made and, of these, 76 (48.4%) were positive. In the other group, 546 cultures were obtained after treatment had begun, and 223 (40.8%) were positive. In order to determine the effect of the blood sulfanilamide level, a separate analysis was made of the children who consistently had levels of 1 mg. or more. Thirty-one patient-seasons were represented in this subgroup, and 87 (43.5%) of 200 cultures were positive. None of the differences is statistically significant.

This experience is greatly at variance with the observations of Thomas, France and Reichsmann,[5] who found that giving sulfanilamide practically eliminated positive beta hemolytic streptococcus throat cultures. Chandler and Taussig[1] found no major difference in the incidence of positive throat cultures between patients in the treated group and those who acted as controls.

Evidence of Toxicity. Toxic symptoms were infrequent and unimportant, as shown in Table 2. Every symptom which could possibly be regarded as evidence of sulfanilamide intoxication has been included. Only 12 (11.2%) of the 107* children who started to take sulfanilamide showed symptoms, and in none was a leukopenia associated. In 2 instances, the drug was permanently discontinued (B.K. and P.Do.). In 3 (M.M., C.O., and C.F.) it was temporarily stopped, and in the remainder it was continued at the same or reduced dosage.

A fall in the white blood cell count below 4500 per c.mm. was observed in 10 (9.2%) patient-seasons. None of these children had subjective complaints suggestive of toxicity. No severe degrees of leukopenia were observed. Details are shown in Table 3. Leukopenia

* This figure includes 18 patient-seasons in which sulfanilamide was used for less than 4 months.

was not observed prior to the second visit, *i. e.*, on the 42d day of treatment. In some cases, it did not appear until as late as the 75th or 101st day of treatment. In 2 patients (R.Z. and J.K.) sulfanilamide was permanently discontinued. In 4 (P.W., N.M., T.B., and D.H. 2) it was temporarily stopped, and in the others it was continued at the same or a reduced dose. It is interesting that 2 patients (D.H. and F.M.) showed leukopenia both seasons.

TABLE 2.—SYMPTOMS SUGGESTIVE OF SULFANILAMIDE TOXICITY

Patient	Sex	Age	Daily dose (gr.)	Symptoms	Day of onset	Blood level (mg./100 cc.)	Subsequent course	Experience other year
B. K.	F	9	15	Transient itching rash of arms; patient's mother discontinued sulfanilamide; rash not observed in clinic	7	..	This was early in our experience and 15 gr. of sulfathiasole daily substituted for balance of year	1 yr.
P. Do.	M	11	15	Patient uncoöperative; nausea and vertigo prompted parent to discontinue drug and withdraw child from study	60	0.2	Previous blood levels 0 and 0; patient not regular in taking drug	Uncoöperative
M. M.	F	9	15	Diarrhea and vertigo for 3 days; patient's mother discontinued drug	120	0.9	Drug resumed with no ill-effects	No difficulty on dose of 15 gr.
C. O.	M	8	10	Skin dry and scaly; hemoglobin 10.5 gm.	133	2.7	Drug discontinued for 2 wks.; then resumed with no further difficulty	1 yr.
C. F.	M	10	15	Somnolence; this continued even when dose was reduced to 10 gr.	60	2.9	Symptoms then entirely relieved by 3 wks. discontinuance of the drug; minor degrees of drowsiness balance of year on doses of 10 or 15 gr.	1 yr.
G. C.	M	12	15	Nausea; patient's mother reduced dose to 10 gr.	30	1.7	Dose again raised to 15 gr., abdominal discomfort resulted; dose reduced to 10 gr., where it remained	No difficulty on dose of 15 to 30 gr.
D. C.	M	6	20	Moderate nausea and vomiting	112	5.9	Dose reduced to 10 gr. with no return of symptoms	1 yr.
P. M.	F	7	15	Slight nausea and vertigo	28	0.5	Dose reduced to 10 gr.; 4 wks. later again complained of nausea; same dose (10 gr.) continued without further difficulty	1 yr.
R. S.	M	4	10	Nausea, vertigo, somnolence	140	3.4	Previous sulfanilamide levels of this height had not been associated with symptoms; dose reduced to 5 gr. with no further ill-effects	1 yr.
P. Di.	F	6	15	Nausea for first 2 or 3 days	1	2.7	Dose kept at same level and no further complaint	1 yr.
M. S.	F	13	20	Slight nausea for 1 day	40	0.4	Same dose continued; again slight nausea on 153d day when sulfanilamide level was 0.3; no subsequent difficulty with blood sulfanilamide level of 1.1 mg.	No difficulty on dose of 15 gr.
D. V.	F	10	15	Nausea for 3 days; faint macular rash with brownish cast of both axillæ	21	0.5	Same dose continued without further trouble	1 yr.

TABLE 3.—LEUKOPENIA

Patient	Sex	Age	Daily dose (gr.)	Blood picture	Day of onset	Blood level (mg./100 cc.)	Subsequent course	Experience other year
R. Z.	M	8	15	WBC 4400 Granulocytes 56%	42	1.6	Same dose continued; increased to 20 gr. 4 wks. later when WBC 5050 and blood level 0.5 mg.; 6 wks. later WBC 3250, granulocytes 36%; blood level 2.8 mg.; dose of 20 gr. continued; 4 wks. later WBC 3450, granulocytes 56%; sulfathiazole in daily doses of 15 gr. substituted for balance of season; no further leukopenia	1 yr.
J. K.	M	12	15	WBC 3900 Granulocytes 49%	49	1.7	Continued at same dose; no leukopenia until 3½ mos. later when WBC 3900, granulocytes 28%; drug discontinued and WBC rose to 4800 with 43% granulocytes 2½ mos. after drug withdrawn	1 yr.
P. W.	M	4	15	WBC 3950 Granulocytes 21%	42	2.7	Drug discontinued 1 wk.; resumed at dose of 15 gr.; later varied from 5 to 10 gr., depending on blood sulfanilamide level; no return of leukopenia	1 yr.
N. M.	M	12	20	WBC 4300 Granulocytes 47%	56	1.7	Drug discontinued for 1 wk. after which WBC 5100; dose 10 to 30 gr. balance of year; no further leukopenia	1 yr.
T. B.	M	5	10	WBC 3750 Granulocytes 39%	56	0.1	Drug discontinued 3 wks. after which WBC 8800; dose of 10 gr. continued remainder of year; blood sulfanilamide as high as 1.6 mg. with no leukopenia	Dose 10 gr.; no leukopenia; av. blood sulfanilamide level 2.7 mg.
D. H. 1	M	7	10	WBC 3500 Granulocytes 51%	42	1.8	Dose of 10 gr. continued; 4 wks. later WBC 6000; dose later increased to 15 gr.; no leukopenia	Leukopenia following year; see below
D. H. 2	M	8	10	WBC 3900 Granulocytes 27%	56	2.9	Drug discontinued; resumed 4 days later; 5 wks. later WBC 7900; 4 wks. later, dose increased to 15 gr.; 7 wks. later on last visit of season, WBC 3600, granulocytes 53%, sulfanilamide level 0.2 mg.	Leukopenia; see above
F. M. 1	M	5	15	WBC 4400 Granulocytes 25%	75	0.2	Dose of 15 gr. continued; 4 wks. later WBC 7000; dose of 15 or 20 gr. used after with no leukopenia; blood level prior and subsequent to this episode 1.1 to 3.3 mg.	Leukopenia following year; see below
F. M. 2	M	6	15	WBC 4400 Granulocytes 55%	63	0	Dose reduced to 10 gr. thereafter; blood sulfanilamide levels of 1.4 to 2.5 mg. with no leukopenia	Leukopenia; see above
C. G.	M	10	20	WBC 4100 Granulocytes 39%	101	2.1	Lost contact with this patient	No leukopenia

Some degrees of anemia were observed in both groups with the hemoglobin occasionally falling as low as 10.5 gm. Anemia was no more frequent among treated than control patients. The administration of ferrous sulphate satisfactorily controlled the anemia in every case.

Discussion. This series of 89 sulfanilamide treated patient-seasons without a recurrence takes on greater significance when it is added to the other favorable reports in the growing literature. The relatively low incidence (7.2%) of recurrences among control patients is difficult to explain. In the light of previous experience with rheumatic fever in Milwaukee, this favorable relapse rate was unexpected. Major, minor and questionable rheumatic episodes combined occurred in 13 (38.2%) of the control patients as compared with 19 (21.4%) of the treated children. The difference is statistically significant and justifies the

conclusion that the drug was beneficial. Sulfanilamide did not affect the incidence of throat cultures positive for the beta hemolytic streptococcus. The reason for this variation from the findings of Thomas, France and Reichsmann[5] is not evident. Further study is indicated.

It now seems clear that sulfanilamide can be given in small, daily doses over long periods without serious ill effects. Suggestively toxic symptoms or leukopenia made it necessary to discontinue sulfanilamide permanently in only 4 (3.7%) of 107 patients who started taking the medication. This confirms the results of all other workers except Stowell and Button.[3] Using somewhat larger doses, they observed one death due to agranulocytosis and a number of less severe toxic reactions.

Summary. Sulfanilamide in small, daily doses was given to rheumatic children in the Cardiac Clinic of the Milwaukee Children's Hospital during the autumn, winter and spring of 1941–42 and 1942–43. Altogether, 89 patient-seasons are represented in the treated group and 42 patient-seasons in the control series. No rheumatic recurrences appeared among the children who took sulfanilamide. There were 3 (7.2%) major and minor recurrences among control patients. Questionable rheumatic episodes were observed with greater frequency in the control group. The incidence of positive beta hemolytic streptococcus throat cultures was approximately the same in the two groups. Manifestations of sulfanilamide toxicity were neither frequent nor severe. Sulfanilamide is recommended as a relatively safe and effective prophylactic measure against recurrent rheumatic infection.

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A STUDY OF SULFONAMIDE AEROSOL INHALATION

A Supplemental Note

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The utilization of the respiratory tract as a route of administration of drugs, notably the sulfonamides, and the effects produced by inhalation of these drugs in the therapy of upper respiratory tract infections,

are the subjects of the present report. An earlier paper[3] dealt with sulfonamide concentrations in the blood of mice which had inhaled sulfonamides in mists produced by the atomization of gelatin-prepared suspensions of the drugs. Technical difficulties in achieving uniform blood levels by this method led to experimentation with smokes composed of crystals.

The purpose of this study was to determine whether or not: (1) inhalations of the drug would be the equivalent of topical application in the respiratory tract, supplying a high concentration of the drug to the infected site; (2) this might prove so efficient that a high level of the drug throughout the body would not be necessary; and (3) absorption of the drug would occur. These 3 questions appear to have been answered in the affirmative.

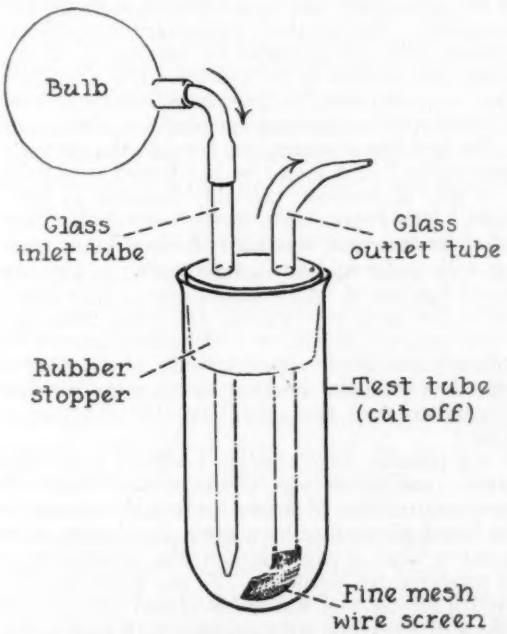

FIG. 1.—Simple type of powder blower for microcrystalline sulfadiazine.

Method. To produce the smoke efficiently from such cohesive powders as the microcrystalline sulfadiazine, it was necessary to make special powder blowers. The simplest of the many types used is shown in Figure 1. Essentially, it is a small bottle with an inlet arranged to blow across the mouth of an outlet tube, which latter is covered by fine-mesh wire screen. An atomizer bulb supplies a sufficient airstream. The blower contains the sulfonamide powder diluted with sea sand. The drug adheres to the sand and on agitation by the airstream is freed gradually from it as the sand is dashed about. This results in a fine smoke from which the sand is filtered by the screen on the outlet tube. The sand's activity and the direction of the inlet airstream keep the screen clear.

This device could not be employed in the experimental work on animals, since its concentration of smoke fell off logarithmically with the quantity of the drug remaining in the blower. For this reason a blower with a constant

feeding device was employed. However, for clinical purposes, the simple blower was suitable and gave satisfactory uniformity of blood levels.

The crystals employed in this investigation included the microcrystals of sulfadiazine and sulfathiazole and the macrocrystals of these sulfonamides and of sulfapyrazine. Their sizes were not constant, but the average diameter of the microcrystals of sulfadiazine used was approximately 2 micra; of the microcrystals of sulfathiazole, approximately 4 micra; of the microcrystals of sulfapyrazine, approximately 3 micra; of the macrocrystals of sulfadiazine, approximately 25 micra; of the macrocrystals of sulfathiazole, approximately 50 micra.

Attempts were made to determine the depth of penetration of the crystals into the lung in order to determine the point of their absorption. Lung preparations dried by means of blowing an airstream into the trachea of the excised lung showed high drug concentrations in the lung periphery but failed to define their source, *i. e.*, whether in air, lymph, or blood channels. After substituting various materials, including dyes, for the crystals in the inhaled air, it was found that carbon particles of comparable size were visible on sectioning the lung. Those smaller than 5 micra in diameter were seen in large numbers in the bronchioles and in the alveoli, as would be expected from the work of Bloomfield.[1] The particles were detected in the air spaces only.

Sulfonamide smoke was administered by passing it through a dynamic chamber containing the animals to be treated. For a single mouse a small bottle was utilized as a chamber, and for large numbers, a rubber-gasketed box was used. Atmospheric pressure surrounding the animal was never above normal. The problem of absorption through the gastro-intestinal route was discussed previously, but it might be mentioned here that the mice had little tendency to lick themselves, probably because so few crystals were deposited on them. The sulfonamide levels were determined according to the micromethod of Bratton and Marshall[2] on blood taken from the tail after careful cleansing with water and alcohol separately. The duration of the exposures to the smokes was at first several hours. This time was decreased to 10 minutes after the early experiments and later reduced to 5 minutes, which exposure was adopted as routine. Concentrations of the smoke were varied by employing quantities of 100 to 300 mg. of the drug to 5 gm. of the sand. Blood was taken immediately after the exposure (which time was never greater than 15 minutes after the animal left the chamber) and at stated intervals thereafter.

To determine the possible local changes resulting from inhalation of the sulfonamide crystals, rats, guinea pigs, and mice were used. They were subjected to various concentrations of smoke for periods varying from 5 minutes to 9 hours. The histologic picture even after the longest of these exposures showed nothing more than a slight hyperemia, which was no more than might have been produced by sacrifice. The mortality rate of those exposed animals which were otherwise well, was not increased over a period of 2 months. Drug concentrations in the blood were reached with approximately the same rapidity in all species used. Blood levels were found to be comparable in normal rats and in others whose noses were closed by sutures. A similar study on mice gave similar results.

Attempts to produce sensitization by inhalation of the crystals were made unsuccessfully in guinea pigs, of which 6 were subjected to the sulfonamide smoke at 2 and 3 week intervals with negative results. This means little, because the type of sensitization that occurs in man has never been reproduced in animals.

One hundred and seventy-three mice were divided into groups of 1 to 20 in number and exposed for 5 minute periods every 3rd day for 2 to 4 weeks. Blood levels were determined on 2 or more of each group at the later described intervals.

Significant differences between the blood concentrations established by the various sulfonamides were not detected; usually the smaller crystals gave higher immediate blood levels.

The bloods taken within 15 minutes of a 5 minute exposure showed 3.4 to 7 mg. of the drug per 100 cc. of blood. Ten minute exposures produced concentrations of the same order of magnitude; 30 minute exposures produced 12 to 18 mg. per 100 cc.; 1 hour exposures, 18 to 22 mg. per 100 cc.; and 2 hour exposures 50 mg. per 100 cc. The mice having a longer exposure time, obviously had a longer absorptive time.

In those mice subjected to an exposure of 10 minutes or less, the concentration in the blood climbed for approximately 6 hours to a point nearly double that of the immediate value. In 24 hours, the level fell to 75% of the immediate value and in 48 hours, it was one-half of the immediate value. The concentration of the smoke, hence the blood levels, varied with the amount of drug employed in the blower. For example, a mouse exposed for 5 minutes to the smoke from a blower which contained 100 mg. of the microcrystalline sulfadiazine had a blood level of 14 mg. per 100 cc. in 1½ hours; another exposed similarly but with 200 mg. in the blower, had a blood level at the same time of 28 mg. per 100 cc., while a third with 300 mg. revealed a blood level of 39 mg. per 100 cc.

The sulfonamides have been administered by this route to approximately 100 persons with various bacterial infections of the respiratory tract. Accurate evaluation of this therapy is not possible at this time. However, several points of interest have presented themselves. First, there has been no evidence of drug reaction although asthmatics were included in the series. Inhalation of the large crystals produced a severe cough not unlike that seen with a foreign body in the lung. The cough lasted approximately 2 hours in the few cases in which large crystals were used. This cough, which was the only unfavorable symptom observed, was never noticed when the small crystals were employed. Second, an analgesic effect previously commented upon in experimental work with burns, was noted by many of the patients, particularly those with pharyngitis or laryngitis. This effect usually lasted 2 or 3 hours. Lastly, purulent nasal discharges frequently cleared in a few hours temporarily, and the duration of all symptoms appeared to be shortened. Blood samples from 5 volunteers were obtained from vein and finger-tip after warming the hand in water (Table 1). The first determination was made within 30 minutes after the subject had inhaled deeply 3 breaths of sulfapyrazine from a blower. The values on any subject at a given time were within 1 mg. per 100 cc. of the others obtained at the same time.

TABLE 1.—SULFAPYRAZINE BLOOD LEVELS IN 5 VOLUNTEERS AFTER INHALATION

	½ hr.	5 hrs.	12 hrs.	18 hrs.	24 hrs.	48 hrs.
Venous blood	2.0	5.5	3.6	1.6	1.4	1.4
Fingertip blood	3.5	..	..	2.5	2.6	1.5

Drug concentrations in the blood of one of us were determined on 8 occasions over a period of more than 6 months while these experiments were in progress, and the exposure to the smoke, while unintentional, was frequent.

Determinations usually were made on Monday mornings after a day

away from the laboratory because sulfonamide-free blood was desired for other purposes. The drug levels, however, varied between 2 and 7 mg. per 100 cc. on every occasion.

Discussion. The sulfonamides are absorbed rapidly into the blood with little or no irritation visible on histologic sections of the lung of small animals. Whether the drug is absorbed directly by the capillaries or secondarily to them from the lymphatics is not clear. The second possibility is probably the more important one, as a reservoir seems to be maintained somewhere in the respiratory tract for a period of at least 6 hours.

Although in this series there is no evidence of sensitivity to the drug or other serious reaction, it is not suggested that this route has a detoxifying effect or that it is safer to administer sulfonamides by inhalation than by other routes. Instead, because of the rapidity with which high blood levels are attained, extra care should be used in the selection of patients in order to avoid any chance of drug reactions.

Summary and Conclusions. The blood concentrations of the sulfonamides when administered as aerosols by inhalation and the treatment of upper respiratory tract infections by this method, have been presented. Crystalline sulfonamides, blown from a simple blower, were inhaled and their rapid appearance in the peripheral blood has been shown.

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SULFADIAZINE AND ITS SODIUM COMPOUND IN TREATMENT OF MENINGOCOCCIC MENINGITIS AND MENINGOCOCCEMIA

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The object of this paper is to record the experience of the Service for Acute Infections of the Central Nervous System of the New York Cith Health Department with sulfadiazine and its sodium compound in the treatment of 141 cases of meningococcic meningitis. Of these, 139 recovered and only 2 died, a mortality of 1.4%. There were in addition 8 cases of meningococcemia without evidence of meningeal involvement, all of whom recovered.

These patients were seen between Jan. 12, 1942, and May 4, 1943. During this period we saw a total of 221 bacteriologically proved cases

of meningococcic meningitis. Eighty of these had been treated with a sulfonamide other than sulfadiazine, by a combination of sulfonamides, or by a combination of sulfonamide and serum. These cases have not been included in this series. The remaining 141 cases, which were treated with sulfadiazine alone, constitute a consecutive series for the use of this drug and form the subject of this report.

Most of these patients were seen by us shortly after the onset or relatively early in the course of the disease. In many instances, however, we were first consulted after the patient had developed a complication or had apparently failed to respond to the chemotherapy.

Clinical Aspects. Table 1 shows the age distribution of the patients in this series. For the purpose of comparison we have also included in this table the age distribution of the 80 cases treated with other sulfonamides or sulfonamides and serum.

TABLE 1.—THE AGE DISTRIBUTION OF 141 CASES OF MENINGOCOCCUS MENINGITIS TREATED WITH SULFADIAZINE ALONE AND OF 80 CASES TREATED WITH OTHER SULFONAMIDES OR WITH SULFONAMIDES AND SERUM

Age (in years)	Cases treated with sulfadiazine alone	Cases treated with other sulfonamides or with sulfonamide and serum
Under 1	6	1
1–10	37	6
11–20	40	22
21–30	20	24
31–40	21	11
41–50	8	11
51–60	6	4
61–70	3	1
	141 cases	80 cases

The duration of illness before treatment with the drug varied from 1 to 8 days. As shown in Table 2, 126 of the 141 patients were treated within the first 3 days of illness.

TABLE 2.—DURATION OF ILLNESS BEFORE CHEMOTHERAPY

Days before chemotherapy	1	2	3	4	5	6	7	8
Number of cases	69	38	18	9	4	2	0	1

Most of the patients presented the typical picture of meningitis on admission, including nuchal rigidity and positive Brudzinski and Kernig signs. Twenty-six of the patients were mentally clear and 115 showed definite changes in the mental state, varying from irritability and apathy to delirium and coma. A hemorrhagic eruption was present in 92 cases. Arthralgia or arthritis was observed on admission in 9 instances. The individual patients showed considerable variation in the severity of the disease, but most of them appeared critically ill on admission and some even moribund.

The 8 cases of meningococcus bacteremia without evidence of meningeal involvement, showed the usual septic temperature and the presence of an extensive hemorrhagic or polymorphous eruption. Arthralgia was present in 4 instances. The spinal fluids were essentially normal.

Bacteriologic Diagnosis. Diagnostic lumbar punctures were performed on all of the cases of meningitis on admission. The cerebrospinal fluid showed varying degrees of turbidity. The cells were greatly increased in number with polymorphonuclears predominating. In a majority of instances the protein content was moderately to greatly increased. The sugar was either absent or markedly diminished in almost all instances, although in a few cases seen early in the disease the sugar content was within the normal range.

The diagnosis was confirmed bacteriologically in all cases. Stained smears of the cerebrospinal fluid showed varying numbers of intracellular and extracellular Gram-negative diplococci in 123 instances. Meningococci were grown from the fluid in 110 of the 131 cases in which cultures were made. In 95 cases the organisms were found both by smear and culture. In 3 instances with spinal fluid findings indicative of purulent meningitis but absence of organisms by smear and culture, bacteriologic diagnosis was confirmed by recovering meningococci from the blood cultures. Blood cultures were made in 85 of the cases of meningitis and were positive in 32 instances. The blood culture was positive in the 8 instances of meningococcemia without evidence of meningitis.

The strain of meningococcus was identified in 99 of the cases of meningitis and in the 8 cases of meningococcemia without meningeal involvement. The organisms were typed directly from the spinal fluid by the Quellung method in 28 instances. In 20 cases, the meningococci obtained from the spinal fluid cultures were agglutinated by type specific sera. In the remaining 59 instances, the type was determined by agglutinating known strains of meningococci with the serum of the patient. Of all these strains, 103 were Type I, 1 was Type II, and 3 were Type IIA.

Method of Treatment and Dosage. All the patients were treated with sulfadiazine, its sodium compound, or a combination of both. With the exception of 1 of the fatal cases (Case 1 below) in which, after a thorough trial of sulfadiazine, 11 gm. of sodium sulfapyridine were administered shortly before death, none of the patients received any other sulfonamide drug and none received serum. While not all of the patients were treated in a strictly uniform manner, the method of therapy that we have adopted was employed in a majority of instances. In general, we have used the following scheme of dosage: On the first day of treatment, children under 1 year of age received from 2 to 3 gm.; children from 1 to 3 years of age received from 3 to 4 gm.; children above that age received from 4 to 7 gm.; and adults from 9 to 12 gm. One-quarter to one-third of this amount was given as the initial dose and the remainder divided and administered at intervals of 4 hours.

In 89 instances the drug was given by vein during the first 12 to 24 hours, as a rule in a 5% solution in distilled water. In very severe cases the parenteral medication was continued for a longer period of time. In the remaining cases the drug was administered orally from the start. It is our belief that the parenteral route should be reserved for the severe cases and for those patients who are unable to take or retain oral medication. There is no indication for the use of the drug intrathecally. In our opinion it is dangerous to make the first dose a massive one, especially when given by vein. Similarly, it is undesirable to give large amounts of the drug simultaneously by vein and by mouth. Following the first 12 to 24 hours, the patient is as a rule able to take medication orally, and he continues to receive the drug at 4 hour intervals.

In the use of the drug after the 1st day, we are guided by the clinical condition of the patient and the concentration of the sulfadiazine in the blood.

It is essential that during the course of sulfonamide therapy the patient should receive a sufficient amount of fluid to maintain an adequate renal output, particularly when large amounts of the drug are administered intravenously. We agree with Dowling and Lepper[8] in recommending the administration of at least 3000 cc. of fluids a day in order to insure a urinary output of 1200 cc. or more daily. This is of particular importance in cases of meningitis because of the danger of dehydration from vomiting early in the course of the disease.

Concentration of Sulfadiazine in the Blood and Cerebrospinal Fluid. We wish to stress the importance of making frequent determinations of the sulfadiazine level in the blood, since its concentration in the blood and cerebrospinal fluid of a given patient is not definitely predictable on the basis of dosage. While there is no conclusive evidence of a definite correlation between the effectiveness of sulfadiazine and its concentration in the blood and cerebrospinal fluid, nevertheless we have obtained prompt and consistent results with drug levels ranging from 10 to 15 mg. per 100 cc. in the blood and from 7 to 10 mg. per 100 cc. in the cerebrospinal fluid. Excessive concentration may lead to drug intoxication. Although some patients can tolerate high concentrations of the drug without untoward effects, the maintenance of a high sulfonamide level is distinctly hazardous. While emphasizing the importance of optimal drug levels, we recognize that some patients may show a satisfactory clinical response to relatively low concentrations. In such instances it is, of course, unnecessary to increase the amount of sulfadiazine.

Long[16] and Finland and his collaborators[9] have pointed out that sulfadiazine readily enters the cerebrospinal fluid and maintains a level of about two-thirds to four-fifths of that found in the blood. Determinations made on comparative blood and cerebrospinal fluid levels in 14 instances would seem to support these observations, as shown in Table 3. In joint exudates the concentration of the drug more nearly approximates that of the blood.

TABLE 3.—THE COMPARATIVE CONCENTRATION OF SULFADIAZINE IN THE BLOOD AND CEREBROSPINAL FLUID

Concentration in mg. per 100 cc.	
In blood	In spinal fluid
6.8	5.5
7.6	5.3
9.0	5.0
9.0	8.8
9.3	8.7
11.3	12.2
12.0	8.0
14.0	7.5
15.0	9.5
15.5	10.2
19.8	15.8
23.0	15.0
28.7	24.0
31.0	17.0

$$\text{Average} = \frac{15.1}{10.9}$$

The concentration in the spinal fluid averages 72% of that in the blood.

Results. The rapidity with which the serious symptoms disappeared in most of the cases was little short of astounding. As a rule, the patients showed striking clinical improvement on the 2nd or 3rd day of chemotherapy. In most instances the fever dropped by crisis (Fig. 1) or by rapid lysis. Occasionally the lysis was slower. While subjective improvement was apparent early, the abnormal neurologic signs usually persisted for a longer period. Indeed, nuchal rigidity not infrequently lasted well into convalescence.

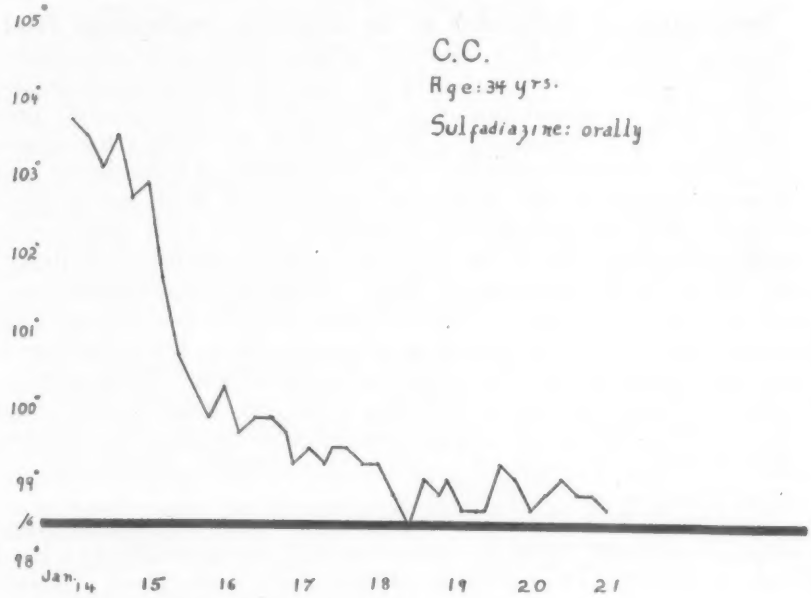

FIG. 1.—Typical fall in temperature by crisis.

Following the initial response, there was usually progressive clinical improvement and the temperature remained normal. Subsequent elevations in temperature were as a rule indicative of either a drug intoxication or the development of a complication. These features will be discussed in detail in another section of the paper.

There is at present a great deal of uncertainty with regard to the duration of the chemotherapy and the total amount of drug required in each case. Early in our study, the administration of sulfadiazine was continued for about 4 to 5 days after the temperature had become normal. More recently, we have found that one may safely discontinue chemotherapy after the patient has been afebrile for 24 to 48 hours and has received a total of 15 to 20 gm. of the drug. We do not think it is necessary to use more than that amount of sulfadiazine in the average case, although an occasional instance may require a larger quantity. As a matter of fact, we have seen recovery with 12 gm. or less in 16 instances, in 4 of which the patient received a total of only 7 to 8 gm. of the drug. It is unnecessary and may even prove harmful to administer too much of the sulfonamide or to use it too

long. The ill-effects from overtreatment are, in our experience, much more frequent than is generally realized.

The question naturally arises as to when the infection may be regarded as having come under control We have found that, with few exceptions, the disease is well controlled when the patient shows a decided improvement in the mental state, has been essentially afebrile for 24 to 48 hours, and has received a total of 15 to 20 gm. of the drug. As a rule, it is unnecessary to resort to lumbar puncture for the purpose of evaluating the progress of the case. An examination of the cerebrospinal fluid may be indicated in those instances in which the course of the disease is unclear or the cause of a persistent fever is not apparent.

In this connection it may be of value to comment on certain features of the spinal fluid examination. Undue stress is often laid on the importance of the total cell count. We have often discontinued the chemotherapy in the presence of a considerable pleocytosis. A rise in the sugar content of the cerebrospinal fluid and the disappearance of the organisms are the most important determinations. However, control of the infection is not infrequently attained before the return of the sugar to normal. Primary reliance on symptomatic improvement as a guide to drug dosage has not resulted in any relapse or recurrence of the infection in the cases in this series or in any of our cases treated with other sulfonamides.

We have already mentioned that in this series of 141 cases of meningococcic meningitis there were 139 recoveries and 2 deaths, a mortality of 1.4%. The 8 patients with meningococcemia but without meningeal involvement recovered promptly and completely. It may be noted that if to the series of 141 cases treated with sulfadiazine, we add the group of 80 cases treated with other sulfonamides or with a combination of sulfonamides and serum, we obtain an over-all mortality rate of 3.6%.

It may be of value to comment briefly on the 2 fatal cases of meningitis in the sulfadiazine-treated series.

Case Studies. Case 1. J. V., male, aged 43, was admitted to the hospital on the 2nd day of illness with signs of semistupor and meningeal irritation. The temperature on entry was 100.6° F. and rose rapidly to 102.4° F. The diagnosis was established by spinal fluid findings which showed meningococci by smear and culture. In the first 12 hours a total of 14 gm. of sulfadiazine was administered by vein resulting in a drug level in the blood of 27 mg. per 100 cc. after 21 hours. The temperature dropped to 98.6° F. For some unexplained reason the patient went into a state of shock from which he recovered following a blood transfusion. Sulfadiazine which had been temporarily withdrawn was resumed by mouth on the 4th hospital day and was continued for 5 days during which 26 gm. were administered. The fever persisted, ranging at first from 100° to 101° F. and rising on the 7th day to 104° F. A partial clearing of the mental state during the 6th and 7th hospital days was only temporary and was followed by a progressive deterioration of the patient's general condition. Sodium sulfapyridine (11 gm.) was given intravenously but also without avail. Decubitus ulcers and cellulitis of the left foot developed terminally. Death occurred on the 10th hospital day. A necropsy was not obtained.

The cause of the circulatory collapse in this patient was obscure. It is

obvious that the chemotherapy was too intensive at the start and was probably continued too long. However, this case must be recorded as an instance of failure to respond to sulfadiazine.

CASE 2. M. F., a 40 year old female, suddenly became ill on March 19, 1943, with headache, vomiting, fever and severe chills. The following day she was admitted to the hospital in coma and in a state of circulatory collapse. The temperature was 101.2° F., subsequently rising to 105.6° F. The heart rate was 160 but the peripheral pulse was not obtainable. The systolic blood pressure was 40 and the diastolic was unobtainable. The lungs showed evidence of pulmonary edema. There was a profuse hemorrhagic eruption and there were also subconjunctival and retinal hemorrhages. The neck was rigid and was associated with positive Brudzinski and Kernig signs. There was the suggestion of a right hemiplegia. The deep and superficial reflexes were absent. The cerebrospinal fluid was cloudy, showed 30,000 cells, predominantly polymorphonuclears, a sugar of 10 mg. per 100 cc. and meningococci on smear and culture. The blood culture was positive. The patient was treated with sodium sulfadiazine by vein, receiving in divided doses a total of 9 gm. However, she remained in coma and in a state of collapse and died 20 hours after admission.

This case obviously belongs to the fulminating type. It is to be noted that no treatment for shock was administered.

In this connection we would like to point out that our series included 3 other cases of the fulminating form, all of which fortunately recovered. These patients were admitted to the hospital in stupor and in a state of shock. Their blood pressures were either low or unobtainable. In addition, they showed varying degrees of meningeal irritation and a profuse hemorrhagic eruption. Meningococci were recovered either from the spinal fluid or from the blood. The patients were treated with sodium sulfadiazine by vein and concurrently for shock with desoxycorticosterone or cortical extract together with plasma or whole blood. Recovery was uneventful in all 3 instances. We do not wish to convey the impression that the outcome in the 4 fulminating cases cited by us represents the recovery rate in this form of the disease, since a number of patients died before they were reported to us or before they could receive appropriate treatment.

It is well known that in the fulminating form of the disease, aside from the extensive hemorrhagic eruption, the outstanding clinical feature is the presence of circulatory collapse. These patients have an overwhelming bacteremia and often show only a minimal degree of meningeal involvement. The most conspicuous necropsy finding is the presence of massive hemorrhages into the adrenal glands. While at the present time the fulminating cases are almost always fatal, it may be hoped that prompt and vigorous therapy for the circulatory collapse, in addition to chemotherapy, may bring about recovery in those instances in which the adrenals are only partly involved by hemorrhage.

Complications and Their Therapy. There were relatively few complications in this series. Arthritis involving one or more joints was the most common of these. It occurred in 15 cases. In 5 instances it was present on admission and in the remaining 10 cases it appeared anywhere from the 3rd to the 8th day. Most of the involved joints showed swelling and tenderness. A suppurative arthritis was relatively uncommon and was as a rule monarticular. The development

of arthritis was an important cause of either a persistent or rising temperature after the 3rd day. The treatment of this complication consisted of immobilization of the involved joint, resumption of the sulfadiazine and, occasionally, aspiration. All of these patients recovered completely.

One patient had a bilateral otitis media on admission. Following myringotomy, the condition cleared up completely. Cystitis was observed in 1 case. One patient developed an extensive left femoral thrombophlebitis on the 11th day. The condition responded promptly to sulfadiazine. There was one instance of uveitis, which was treated successfully with chemotherapy. It may be noted that before the advent of sulfonamide therapy this complication usually led to a panophthalmitis and permanent blindness. The low incidence of serious complications was quite remarkable.

Toxic Effects. Toxic reactions referable to sulfadiazine were encountered in 42 of the patients, 10 of whom had more than one untoward effect.

The most common toxic reactions encountered in this series were related to the urinary tract. Hematuria was observed in 20 patients, in 15 of whom it was microscopic and in 5, gross. Since we have no records of daily urine examinations in every case, it is possible that the incidence of hematuria was somewhat higher. Five of these were accompanied by oliguria or anuria. There were 3 instances of oliguria in which there was no record of a preceding hematuria. As may be seen from Table 4, most of the patients developed a renal complication on the 2nd to 4th day of chemotherapy. In 1 instance hematuria appeared 5 days after the withdrawal of chemotherapy. It may be noted also that the occurrence of these untoward reactions was not definitely attributable either to the total amount of drug used or to its level in the blood. Keitzer and Campbell[13] and Dowling and Lepper[8] believe that a diminished urinary output is probably an important factor in the causation of the renal complications. Although we do not have precise information on fluid balance in our series, it is our impression that this opinion is warranted. It is of importance, therefore, to maintain a urinary output of at least 1200 cc. in each 24 hour period.

The nature of the renal damage is at present not entirely clear. Several observers[1,5,21] have pointed out that there are 2 types of renal lesions, namely a mechanical blockage of the urinary passages by concretions of crystals, and toxic effects on the tubular epithelium. Leutcher and Blackman[15] have recently reported the finding of glomerular damage in 2 instances of sulfonamide intoxication.

Most of our renal reactions cleared up rapidly following the early institution of conservative measures. These included the immediate withdrawal of the drug, forcing of fluid and the application of heat to the back and the abdomen. In 2 instances, obstruction of the urinary tract resulting from the deposition of sulfadiazine crystals was relieved promptly by ureteral catheterization and pelvic lavage. In most of our cases the hematuria cleared up within 48 hours after the drug was

stopped. The finding of even a few red blood cells in the urine may be regarded as a danger signal and as an indication for the withdrawal of the sulfadiazine. This is a very important precautionary measure and indicates the need for daily urine examinations. It is safe to resume the chemotherapy, if necessary, 12 to 24 hours after the urine has cleared, as was demonstrated in 4 of our cases. There is growing clinical evidence[11,12] that alkalinization of the urine increases the solubility of the drug and decreases the likelihood of renal reactions, particularly of the obstructive type. However, the presence of crystals in the voided urine should not be considered an indication for stopping chemotherapy provided the urinary output is good.

TABLE 4.—RENAL REACTIONS FOLLOWING SULFADIAZINE THERAPY

	Chemotherapy prior to reaction					
Case	Amount of drug (gm.)	No. of days drug was given	Blood concentration (mg./100 cc.)	Nature of reaction	Clearing of urine (days	Remarks
1	69	10	..	Hematuria–gross	..	
2	17	2	10	Hematuria–micro	2	Chemotherapy resumed. Urine remained clear.
3	18	3	17	Hematuria–micro	3	
4	20	2	17	Oliguria with micro–hematuria	..	Microscopic hematuria, albuminuria. Edema. Pelvic lavage.
5	12	1	11.1	Oliguria with micro–hematuria	4	Azotemia. Ureteral catheterization. Impaction washed out.
6	19	4	..	Hematuria–micro	3	Chemotherapy continued for 2 days more. When discontinued, urine cleared.
7	22	2	8.3	Hematuria–micro	2	Arthritis. Chemotherapy resumed. Urine remained clear.
8	30	5	14	Hematuria–micro	1	
9	7	1	11.2	Hematuria–gross	1	
10	30	3	..	Hematuria–micro	..	
11	22	4	..	Hematuria–micro	2	
12	16	2	..	Hematuria–gross	2	Renal pain.
13	3	1	21	Oliguria with micro–hematuria	..	Began after 3 gm. of sulfadiazine by vein. Chemotherapy continued. Oliguria on 3d day. Azotemia. Chemotherapy cut on 7th day. Urine cleared.
14	10	2	11	Hematuria–micro	2	
15	17	2	7.6	Hematuria–micro	4	
16	14	2	..	Hematuria–micro	..	Hematuria appeared 4 days after chemotherapy discontinued.
17	14	2	11.2	Oliguria	2	Increased fluid intake. Oliguria cleared. Arthritis. Chemotherapy continued.
18	10	2	..	Oliguria with hematuria–gross	2	
19	12	2	50.2	Oliguria	..	Edema. Improvement rapid.
20	6	1	41.4	Hematuria–gross	1	
21	12	2	9.1	Oliguria	..	No hematuria.
22	9	1	..	Oliguria with hematuria–micro	..	Followed by oliguria and edema with transient hypertension as chemotherapy was continued and level rose to 46 mg. %. Chemotherapy then stopped; urine cleared.
23	6	1	14.7	Hematuria–micro	1	Began 7 hours after chemotherapy started.

The second most important toxic effect that we have encountered in our series was drug fever, which was noted 15 times. In 8 patients it occurred alone and in 7, in conjunction with some other form of intoxication. When the drug fever appeared alone, its onset was as a rule early in course of treatment. It is probable that this complication

was even more frequent than is indicated by our figures, since its recognition is often difficult. Contrary to the general belief that this reaction occurs toward the end of the 1st week, we have usually noted its appearance as early as 24 or 48 hours after the beginning of chemotherapy. This early drug fever was suspected when, after the initial defervescence, followed by a short period of clinical improvement varying from a few hours to 1 or 2 days, the patient became subjectively worse and the temperature rose (Fig. 2). The ascent of the fever was usually step-like or irregular in manner. In all but 1 of the cases the fever persisted as long as the chemotherapy was continued. Withdrawal of the drug resulted in a fall of the temperature by crisis in all but 1 instance. In this exceptional case the defervescence was by lysis lasting 4 to 5 days. There was 1 instance in which the fever developed on the day the drug was discontinued and, following a course of 2 days duration, dropped by crisis.

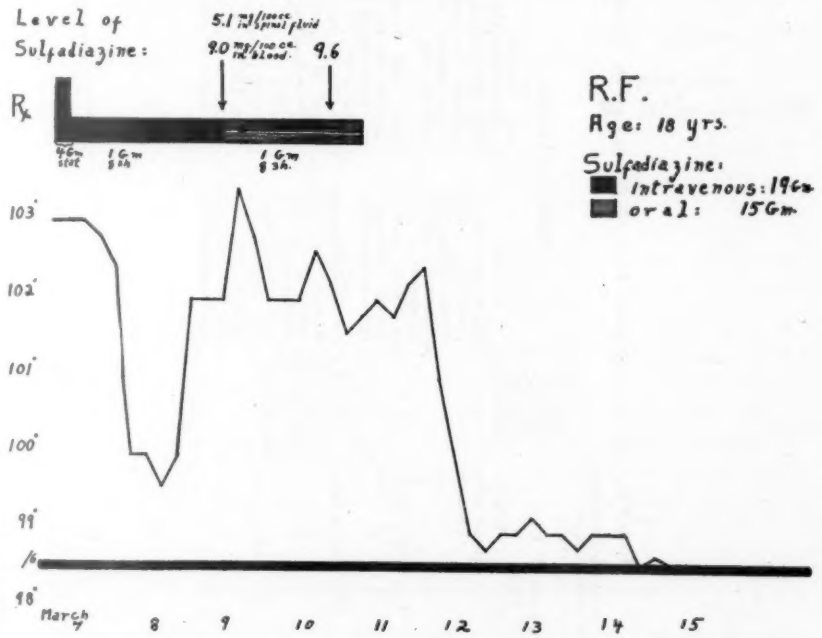

FIG. 2.—Temperature curve indicating the early appearance of drug fever.

When it is difficult to decide whether the secondary rise in temperature is the result of drug intoxication or the persistence of the infection, assistance may be obtained from lumbar puncture. If the cerebrospinal fluid findings show evidence of improvement such as a drop in the cell count, an increase in the sugar and an absence of organisms, one may safely withdraw the drug. On the other hand, if the spinal fluid findings indicate a still active infection it is necessary to continue the chemotherapy.

Although there is a growing body of evidence indicating that all

TABLE 5.—ENCEPHALOPATHY DUE TO SULFADIAZINE INTOXICATION

Case	Age (yrs.)	Symptoms of encephalopathy	Chemotherapy prior to onset of complication: No. of days drug given	Chemotherapy prior to onset of complication: Amount of drug (gm.)	Chemotherapy prior to onset of complication: Route	Level of drug in blood (mg. per 100 cc.)	Spinal fluid findings: On entry	Spinal fluid findings: During encephalopathy	Course and outcome
1	37	Mounting fever; delirium with hallucinations	2	20	10 gm. intrav. 10 gm. oral	26.4	Cells: 26,000 (polys); protein: 4+; sugar-absent; smear: meningococci; culture: meningococci	Cells: 2300 (lymphos); protein: 4+; sugar: 3+; smear: neg.; culture: neg.	Drug cont. 6 days; symptoms persisted, with mounting fever and clearing spinal fluid. When drug was stopped temp. dropped sharply from 105° F. to normal with prompt clin. improvement.
2	1	Moderate fever, convulsions, coma	3	11	4 gm. intrav. 7 gm. oral	31.0	Cells: 3150 (polys); protein: 2+; culture: meningococci	Cells: 2500 (polys); protein: 36 mg./100 cc.; sugar: 80 mg.; no organisms	Drug cont. 9 days. Remained in semi-stupor and developed blindness and deafness. When drug was stopped, gradual improvement. Later return of vision and hearing; persistence of convulsions.
3	35	Mounting fever, coma	2	17	All by vein	38.0	Cells: 60,000 (polys); protein: 840 mg.; sugar: ab.; smear: meningococci; culture: meningococci	Cells: 500 (polys); sugar: 50 mg.; no organisms by smear or culture	Drug cont. 7 days with mounting fever and coma. When drug was stopped, temperature dropped by lysis and mental state cleared.
4	44	Rapid rise in temperature, deep coma	2	30	All by vein	15.7	Cells: 6000 (polys); protein: 417 mg.; sugar: 11 mg.; culture: meningococci	Cells: 300 (polys); protein: 120 mg.; sugar: 35 mg.; no organisms by smear or culture	Drug stopped 3d day when temperature was 106° F. Immediate improvement in mental state and temperature dropped to normal in 4 days.

members of the sulfonamide group have a toxic effect on the nervous system, the subject has not received sufficient attention. A number of investigators[3,7,17] have noted the development of injury to the nervous system of animals fed with a variety of sulfonamides. Clinical reports[2,4,6,10,14,18,19,20] indicate that these drugs produce widely varied types of toxic nervous reactions. These include the peripheral neuropathies, deafness, optic neuritis, blindness and other visual disturbances, encephalomyelitis, encephalopathy with or without convulsions, mental confusion, psychoses, and disturbances of speech. Little[14] has emphasized that sulfonamides appear more neurotoxic in the presence of preëxisting disease of the nervous system.

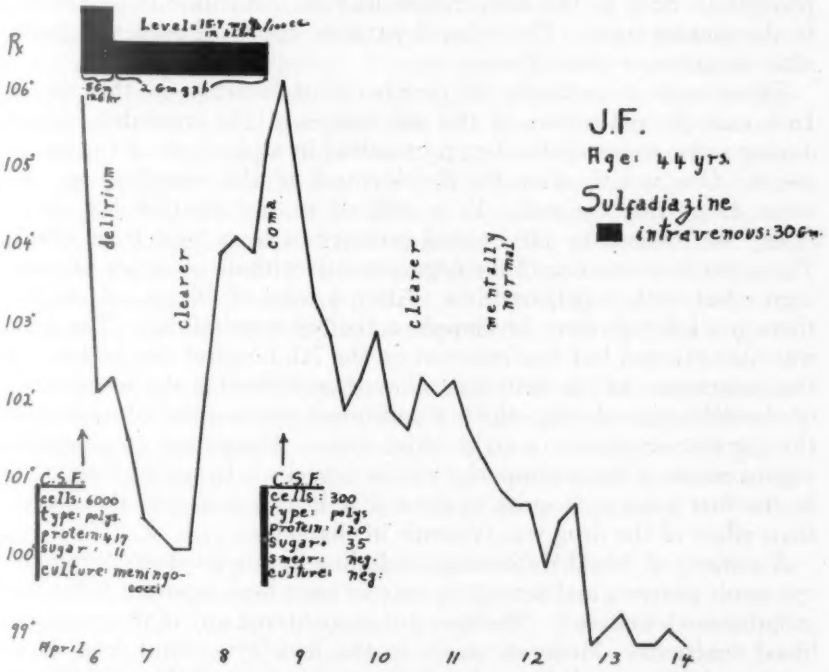

FIG. 3.—Rise in temperature accompanying encephalopathy. Note rapid improvement in clinical picture following withdrawal of sulfadiazine.

We have encountered 4 cases in which drug intoxication produced the syndrome of encephalopathy. This complication is usually difficult to recognize and to differentiate from the symptomatology of the meningitis. Table 5 shows the important clinical features. The onset of this condition was early in the course of treatment, usually appearing on the 2nd or 3rd day. The clinical picture was characterized mainly by varying grades of stupor often progressing to deep coma. Occasionally there were delirium, hallucinations, or convulsions. These symptoms were invariably accompanied by a significant rise in temperature (Fig. 3). It may be noted that the patient with convulsions developed also bilateral blindness without fundus changes together

with bilateral deafness, both of which cleared up late in convalescence. It is our impression that these latter complications were due to drug intoxication, since the blindness and deafness caused by the infection are practically always permanent. One patient developed euphoria and garrulousness during the course of chemotherapy. In 1 case without evidence of encephalopathy there was a transitory unilateral tinnitus, apparently as a result of drug intoxication.

It is important to note that in all of the cases of encephalopathy examination of the spinal fluid during the development of the intoxication showed definite evidence of improvement. This fact was of help in ruling out the infection as the cause of the aggravation of the clinical picture. In 1 of the patients, withdrawal of the drug resulted in a precipitous drop in the temperature and an immediate improvement in the mental state. The other 3 patients improved more gradually after cessation of chemotherapy.

There were 2 instances of peripheral neuropathy in this series. In 1 case the infiltration of the soft tissues of the antecubital space during intravenous chemotherapy resulted in a paralysis of the radial nerve. One month after the development of the complication, the wrist drop still persisted. It is difficult to say whether the nerve injury was caused by mechanical pressure or by a local toxic effect. The other case was one of meningococcemia without evidence of meningitis but with a polyarthritis. After a total of 10 gm. of chemotherapy a left foot drop developed on the 3rd hospital day. The drug was discontinued but was resumed on the 7th hospital day because of the progression of the arthritis. Two days following the resumption of chemotherapy during which 9 additional grams were administered the patient developed a right wrist drop. There was considerable improvement of the neuropathy within 2 weeks. In contradistinction to the first case, it is quite evident that in this instance, the neurotoxic effect of the drug was systemic in character.

A variety of blood dyscrasias, including agranulocytosis thrombocytopenic purpura and hemolytic anemia have been reported following sulfadiazine treatment. We have not encountered any of these serious blood reactions. Moderate drops in the leukocyte count from high or normal figures to below normal occurred in 3 cases (from 22,000 to 4320; 20,950 to 4800; 9000 to 4800). These did not constitute an indication for withdrawal of the drug. There were 3 patients with initial leukocyte counts below 6000 whose counts rose during therapy. In 1 of these, the number of leukocytes rose from 1100 before treatment to 12,000 on the 2nd day of treatment. It is evident that the presence of an initial leukopenia is not a contraindication to the use of chemotherapy.

A skin eruption was noted in 3 patients. This was of the morbilliform type and was associated in each instance with a slight rise in temperature ranging from 100° to 101.8° F. In 1 case the rash appeared on the 2nd day of therapy, and in the other 2, on the 4th day. The total amounts of the drug received prior to the development of the cutaneous eruption were 11, 16 and 30 gm. respectively. The concen-

tration of the drug in the blood was relatively low in all of the cases (5.3, 7.5 and 8 mg. per 100 cc.). It would seem that the development of this complication is not dependent on either the total amount of the drug administered or its concentration in the blood. It should be noted that in each instance the rash disappeared within 24 to 48 hours after the withdrawal of the drug.

We have discussed the toxic reactions at length because a knowledge of these is of basic therapeutic importance. The intelligent planning of dosage and the proper evaluation of the patient's response to chemotherapy are in large measure dependent upon the physician's understanding of the untoward effects. Constant vigilance and the prompt institution of remedial measures upon the earliest appearance of toxic signs will insure the safe use of this very valuable drug.

Failure of Response. We were consulted in 35 cases reported to us as chemotherapeutic failures. Twenty-two of these proved to be instances of some form of drug intoxication. In 11 cases the development of arthritis misled the physician into the belief that the patient was failing to respond to the chemotherapy. The 2 remaining cases were the fatalities described above. The presence of an associated condition such as cardiovascular disease, nephritis, or tuberculosis may interfere with the success of sulfonamides. We are convinced that, excepting those cases which are of the fulminating form or which have a severe associated disease, no patient with meningococcus meningitis or meningococcemia should fail to respond to properly administered chemotherapy.

There is evidence, both experimental and clinical, that under certain circumstances bacteria develop a resistance to sulfonamides. Most of the studies on sulfonamide resistance have been obtained for the pneumococcus. We have not encountered any case of meningococcic meningitis or meningococcemia in which drug fastness appeared to be the cause of failure of response.

In several cases reported to us as sulfonamide failures, we were able by careful and repeated study of the spinal fluid to prove an error in diagnosis. The causative organisms, originally recorded as meningococci, proved to be *H. influenzæ* or Gram-positive cocci which had been overdecolorized during staining. As is well known, meningitis caused by these organisms does not respond to chemotherapy as satisfactorily as the meningococcic form.

Remarks on Serum. In view of the excellent results obtained with sulfadiazine in this series and with other sulfonamides in a large number of cases not included in this study, it is difficult to see what contribution one can expect from the additional use of the specific serum. In cases of apparent failure of response to sulfonamide therapy the use of the specific horse serum has not in our experience produced any striking benefit. We have already pointed out that when sulfonamide therapy does not result in prompt improvement it is necessary to determine and correct the underlying cause of the apparent failure.

Summary and Conclusions. 1. Sulfadiazine and its sodium compound were used in the treatment of 141 bacteriologically proved cases

of meningococcic meningitis and 8 cases of meningococcemia without meningeal involvement.

2. Our method of treatment and dosage have been discussed in detail. We have found that with few exceptions the disease was well controlled and chemotherapy could be safely discontinued when the patient shows a decided improvement in the mental state, has been essentially afebrile for 24 to 48 hours and has received a total of 15 to 20 gm. of the drug.

3. The rapidity with which most of the serious symptoms disappeared was little short of astounding. Of the 141 patients with meningitis, 139 recovered and 2 died, a mortality of 1.4%. The 8 patients with meningococcemia but without meningeal involvement also recovered.

4. There were relatively few complications in this series. The most common of these was arthritis, which occurred in 15 cases.

5. Toxic reactions were encountered in 42 of the patients, 10 of whom had more than one untoward effect. The most common of these toxic reactions were related to the urinary tract. The second most important toxic effect was drug fever, which usually occurred as early as 24 to 48 hours after the institution of chemotherapy. We have encountered 4 cases of encephalopathy resulting from sulfadiazine intoxication in this series. There were also 2 instances of peripheral neuropathy following sulfadiazine intoxication. A morbilliform skin eruption was noted in 3 cases and was associated in each instance with a slight rise in temperature. With the exception of the peripheral neuropathies all the toxic reactions cleared up rapidly following withdrawal of the drug and the institution of remedial measures.

6. In cases of apparent failure of response to sulfonamide therapy the use of the specific horse serum has not, in our experience, produced any striking effect. Most of the cases reported to us as chemotherapeutic failures were instances of intoxication, often the result of overtreatment. We are convinced that, excepting those cases which are of the fulminating form or which have a severe associated disease, no patient with meningococcic meningitis or meningococcemia should fail to respond to properly administered chemotherapy.

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THE CHIEF URINARY PIGMENT

The Relationship Between the Rate of Excretion of the Yellow Urinary Pigment and the Metabolic Rate

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The yellow color of the urine is at once a striking yet poorly understood characteristic.

Some years ago Drabkin[2] described a method for measuring pigment concentration by comparison with a standard dye solution in a colorimeter, and has studied the pigment output in relation to basal metabolic rate. He concluded that the pigment is constant from day to day and that in several species, the pigment output was proportional to the surface area and the urinary pigment output was roughly proportional to the basal metabolic rate in hyperthyroid patients. Drabkin inferred that the urinary pigment was a product of endogenous metabolism, and that the rate of elimination of this pigment was proportional to the intensity of metabolism. Confirmation of this thesis was given in a second paper, among hyperthyroid patients, in some cases both before and after thyroidectomy, and among febrile patients, basal metabolic rates could be correlated with the daily output of urinary pigment. Drabkin[3] did not believe, however, that this correlation was close enough to justify calculation of the metabolic rate from measurement of the urinary pigment.

The present authors have reinvestigated the nature of the relationship between urinary pigment output and the rate of metabolism using other procedures and controls than those employed by Drabkin.

Methods. Our technique for the estimation of the urinary pigment was a purely photometric one. In our earlier work, we used the Pulfrich Stufenphotometer, comparing light intensities through the S43 filter (peak wave length 430 millimicra). This, among 7 filters distributed throughout the spectrum, gave results which were most consistent and most closely related to

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BMR. Latterly, the Klett photoelectric colorimeter was employed, the light passing through the Klett standard blue filter. Both the negative logarithm of the percentage of light transmitted through the solution as given by the Pulfrich instrument and the dial reading given by the Klett instrument were found to be proportional to the relative concentration in samples made by careful dilution of a single urine specimen, thus confirming the fact that Beer's law obtains for our readings. Although we realized that we had not ruled out the possibility of the existence of 2 or more urinary pigments which absorbed blue light, for the purposes of this investigation we defined the yellow urinary pigment as that pigment whose concentration was measured by the negative logarithm of the percentage of blue light (peak 420–430, relatively monochromatic) transmitted through a standard length of urine. For our purposes, this negative logarithm was treated as the concentration itself and the product, the negative logarithm by the volume as the amount of pigment.

The creatinine content of the urine was determined by one of two variations of the Jaffe reaction.[4] In each a mixture of 10% sodium hydroxide, saturated picric acid and urine was made up in the following proportions: (1) 1:3:2 cc.; (2) 1.5:20:1 cc. After standing 10 minutes, the mixture was diluted to 100 cc. and the color intensity compared with that yielded by a standard solution of creatinine (1 mg. per cc.) using the visual colorimeter in the first case and the Klett photoelectric colorimeter with green filter in the second. When the second method was calibrated against known dilutions of the standard solution a smooth curve was obtained characterized by the equation: $2y = x + x^2$, where y represents the known concentration of the sample in mg. per cc. and x represents the apparent concentration. Whereas an error of +15% at a concentration of 0.5 mg. per cc. and −20% at 2 mg. per cc. is implied, most of our results fell between 0.8 and 1.2 where the errors were less than ±6%. These errors were eliminated by means of the calibration curve. No attempt was made to calibrate the first method. It should be pointed out that the proportions of sample and reagents in Method 1 are those originally prescribed by Folin and are known to give correct readings for ratios varying from 2:1 to 1:2. The proportions in the second method were those in current use in the hospital laboratory and contained an excess of picrate, the yellow color of which forms a large part of the total color.

To prevent variations in the apparent concentration of urinary pigment due to chemical change after voiding and to manipulation, the following procedure was adopted: Urine specimens were placed in an icebox immediately after being voided and photometric readings were made as soon as possible, though never later than 2 hours thereafter. Immediately before examination, all specimens, whether or not they appeared clear, were subjected to 10 minutes of high speed centrifugation, which was prolonged, if necessary to clear the urine. Dilutions were made as necessary.

The subjects for the intensive studies were male medical students and young physicians in good health. The subjects of the extensive studies were those patients from a general medical and surgical service for whom estimation of BMR was ordered by the physicians in charge and from whom specimens could be collected. In each case unusual physical activity was avoided on the day before collection of the specimen, and beets and rhubarb were excluded from the diet.

Results. After standing, urines were observed to show apparent increase in concentration of pigment. At room temperature this amounted to more than 10% within 2 hours and 16% within 18 hours; in the icebox the apparent increase was 2% within 2 hours and 6% within 18 hours. Alteration of urinary pH and specific gravity within physiologic limits revealed that no correction for these factors was indicated. Light absorption readings were diminished by at least 10% if the urine was filtered through a single thickness of filter paper.

Four subjects submitted 5 series of specimens at 1- to 3-day intervals. On most occasions 1 specimen of urine was collected upon arising in the morning, the bladder having been emptied last at bedtime, and another was collected after about an hour of rest in basal condition, the bladder having been emptied at the beginning of the hour. The hourly excretion of urinary pigment was calculated by multiplying the pigment concentration by the volume of urine presented and dividing the product by the length of the collection period in hours. The following is a typical series of data (Subject D) for rate of pigment output during overnight and basal periods, respectively (x = not obtained): 47-x, 53-x, 44–54, 49-x, 49-x, 44-x, 45-x, 46–57, 43–45, 48–48, 48–61, 50–64, 38–54, 47–52, 52–71, 60–80, 48–61 and 48–57. The results, including coefficients of variation (*i. e.*, standard deviation divided by the mean, expressed in per cent) are presented in Table 1.

TABLE 1.—CONSTANCY OF HOURLY PIGMENT OUTPUT

	No. of samples		Mean (units per hour)		Standard deviation (units per hour)		Coefficient of variation (%)	
	Overnight	Basal	Overnight	Basal	Overnight	Basal	Overnight	Basal
A (Series 1)	16	5	43.6	48.0	6.1	6.7	14.0	14.1
(Series 2)	14	0	36.7	..	3.2	..	8.7	
B	15	7	49.3	60.4	3.6	10.5	7.3	17.4
C	29	11	51.8	57.0	6.2	4.8	11.9	8.3
D	18	12	45.7	58.7	4.8	8.9	10.4	15.1
							10.5	13.5

To correct for weight, height, habitus and age among the subjects, the rate of pigment excretion was compared to the rate of excretion of creatinine. The ratio pigment concentration/creatinine concentration for Subject A, Series 2 showed a coefficient of variation of 9.4, not significantly different from the coefficient for pigment alone, 8.7. For an afebrile 17 year old girl with a receding pleural effusion, presumably tuberculous, the following series of ratios was obtained during basal periods: 206, 175, 168, 185, 232, 225, 201, 187, 228; this corresponds to a coefficient of variation of 11.1. When 20 24-hour urine specimens donated by a class of male medical students were examined for pigment concentration and creatinine concentration, and ranks assigned; a positive correlation of 0.65 was obtained. In view of these results and because a ratio of concentrations eliminates the necessity of measuring urinary volumes per unit time, always a source of inaccuracy in the absence of catheterization; and because in the presence of thyroid pathology the numerator and denominator are expected to vary in opposite directions, thus giving wider excursions than either alone; the ratio P/C was examined as a possibly useful clinical datum.

By the administration of thyroid extract to the point of toxicity, the basal metabolic rate was varied in the 4 subjects mentioned above, BMR determinations were made every 1 to 5 days, and on those days overnight and basal pigment determinations were made. Each series of data was examined to determine how closely the pigment values paralleled the BMR values, with respect to the trend of the

series, individual fluctuations and maintenance of proper proportions. Ten series of data were obtained; 5 dealing with specimens collected during overnight periods and 5 during basal periods. Of each 5, 2 included creatinine data. The results of a typical experiment are given in Table 2. Whereas the pigment excretion per hour in the basal state gave a slightly better correlation with the BMR, the P/C ratio was considered preferable for reasons given above.

TABLE 2.—RESULTS OF A TYPICAL EXPERIMENT

Date	BMR	Pigment per ½ min.	Creatinine per ½ min. (mg.)	P/C
3/9/42	1	..	..	111
3/11	9	..	..	109
3/13	3	..	..	110
3/16	1	..	..	131
3/18	6	..	..	95
3/20	9	..	..	120
3/23	11	..	..	129
3/27	19	..	..	136
4/1	24	..	..	108
4/3	27	99	0.62	160
4/6	7	76	0.61	124
4/8	20	66	0.53	125
4/10	14	82	0.60	137
4/15	1	70	0.65	108
4/17	14	64	0.65	98
4/20	9	65	0.64	101
4/22	1	70	0.61	114
4/24	2	66	0.72	92

NOTE.—First dose of thyroid extract taken on 3/11, last on 4/2. Urine collected immediately after BMR determination; sample collected one hour earlier discarded.

To test the reliability of single P/C values for the estimation of BMR, urine samples were collected from each of the adult service patients who were scheduled for BMR determination about 1 hour before and immediately after the procedure. P/C was determined for the second sample only. The Klett photoelectric photometer was used. The data for females (Fig. 1) were much more satisfactory than those for males; 63 determinations were included, representing 34 patients. BMR readings varied from 72% of normal to 155% with a mean of 111% and a standard deviation of 20.4%. P/C readings ranged from 143 to 545, averaging 263, with a standard deviation of 112.2. The correlation coefficient, assuming a straight line relationship, was 0.75 (Bernstein, 0.69).* The standard error of estimate was 13.5%. The regression lines are BMR = 59.3 + 0.20 P/C (BMR = 53.9 + 0.22 P/C, Bernstein). Twenty-two observations were made on 15 male patients. Here, there was a much wider dispersion of readings than among female patients. In many of the cases which

* Since Bernstein's linear correlation coefficient[1] and regression are not well known, it may be *apropos* to remark here, that in this system, deviations are not squared, thus avoiding magnification of large errors. The regression lines computed by this method are those which fit the data best according to the method of least squares, if the weight of a deviation is taken inversely proportional to the absolute value of the deviation of the independent variable from its mean. "The method is strongly recommended for all cases in which the data lose reliability with increasing deviations from the mean .... the influence of extreme doubtful readings is considerably lessened."[1]

yielded the most aberrant results, clinical evidence supported the estimate given by P/C rather than the BMR determination itself. BMR values varied from 64 to 153%, averaging 118%, with a standard deviation of 24.8%. P/C readings ranged between 125 and 536 with a mean of 237 and a standard deviation of 112.2. The correlation coefficient of Pearson was only 0.30, while that of Bernstein in which wide variations are relatively devaluated, 0.51. The regression lines are respectively: BMR = 102.3 + 0.067 P/C and BMR = 96.7 + 0.090 P/C.

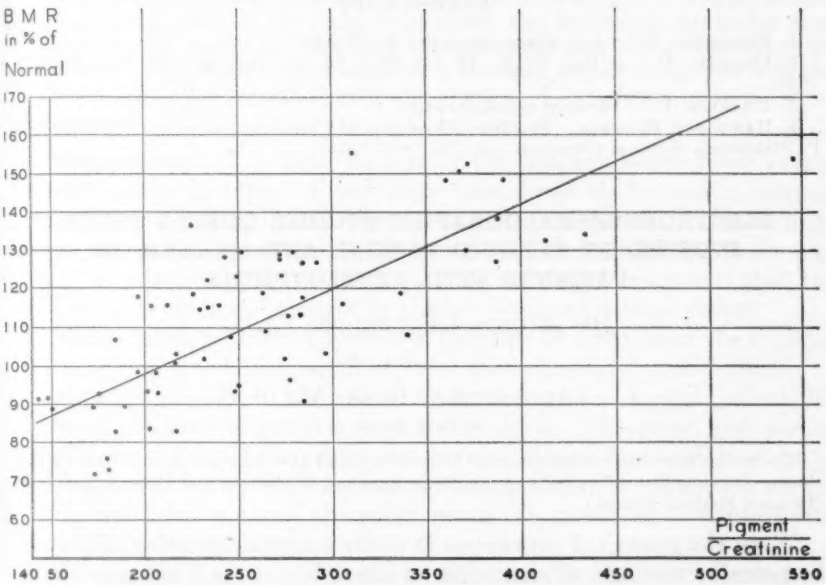

FIG. 1.—Scatter diagram (skedagram) relating BMR with pigment/creatinine among 34 unselected female patients (63 determinations) with least mean square regression line.

These studies constitute an extension and essential confirmation of Drabkin's earlier work.

Summary. 1. The hourly excretion of urinary pigment was constant in any given subject within a coefficient of variation of about 10%, whether measured for an overnight period or for a basal resting period.

2. The same constancy was true of the ratio of the concentration of urinary pigment to that of urinary creatinine. Moreover, among normal males, at least, there was a correlation between the rate of pigment output and the rate of creatinine output; in other words, the concentration ratio P/C was constant among normal males.

3. When the metabolic rate was elevated by the ingestion of thyroid extract, P/C variations paralleled the trend and the fluctuations of the BMR quite closely.

4. Among adult females there was a high correlation between individual P/C values of urine collected during a basal period and the

BMR determined at the end of that period. Among a much smaller number of adult males, the correlation was lower, but this group included a number of observations where the clinical impression was more consistent with the P/C value than with the widely divergent BMR. This circumstance requires further investigation.

It is believed that the P/C ratio applied to a large number of cases may show results of interest. It is also possible that this ratio may be useful as a substitute for the BMR determination when the latter cannot be performed or gives results which are inconsistent with the clinical diagnosis.

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ELECTROENCEPHALOGRAPHIC STUDIES DURING FEVER INDUCED BY TYPHOID VACCINE AND MALARIA IN PATIENTS WITH NEUROSYPHILIS

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With the growth of experience in electroencephalography (EEG), it becomes increasingly evident that an alteration of the EEG may occur in a wide variety of conditions. As a result of our interest in the changes in neurosyphilitic patients occurring during antiluetic therapy, our attention was directed toward a study of the brain-wave patterns during fever. In the preliminary experiments, it soon became clear that striking modifications of the EEG were associated with the height of the fever paroxysm. The present paper is an analysis of the EEG changes during the rise and fall of temperature induced by malaria and/or intravenous typhoid vaccine.

Material and Methods. Twenty-three patients undergoing treatment in the Neurosyphilis Clinic of the Boston Psychopathic Hospital were utilized in this study. The diagnostic classification and number of cases were as follows: general paresis, 13 cases; meningo-vascular syphilis, 3; meningo-vascular syphilis with probable general paresis, 2; tabes dorsalis, 2; optic atrophy, 2, and tabo-paresis, 1. The individual cases varied considerably in the duration and severity of the clinical picture.

Fever was induced by intravenous administration of graduated doses of typhoid vaccine or by inoculation with malaria. The individual doses of typhoid vaccine varied between 50 and 250 million killed suspended typhoid organisms.

EEG tracings were obtained before the temperature rise and at intervals of ½ to 1 hour during the fever. Temperature was taken before and after each

brain-wave recording. Fluids were given freely as requested by the patient and care was taken to keep the patient awake and as comfortable as possible during the period of observation.

Observations on 54 paroxysms of fever were made, 34 of which were induced by typhoid vaccine injection and 20 by malaria.

Malarial paroxysms were generally ushered in by a more severe chill than were those resulting from typhoid vaccine injection. In addition the rise in temperature with malaria was usually more rapid and the temperature peak higher. As a rule, the more sudden and more severe the fever paroxysm by either method of induction, the greater was the subsequent modification of the EEG. For simplicity the data for both methods will be described together.

Apparatus. A Grass 6-channel ink-writing amplifier with a paper speed of 30 mm. per second was employed. Electrodes were applied to frontal, motor, and occipital areas of the right hemisphere, and indifferent electrodes were applied to the mastoids. Simultaneous monopolar and bipolar tracings were recorded. All records were obtained at a standard amplification, and with the use of a filter allowing undistorted reproduction of wave forms up to 50 cycles per second.

Observations. The basic pattern of the patients before fever varied considerably in type. Eight were considered to be within normal limits, 5 were classed as borderline, and 10 as abnormal. The findings were in general agreement with those of Finley, Rose and Solomon[4] who, in a larger group of patients with neurosyphilis, found that the majority of tracings belonged to the borderline-abnormal group.

EEGs taken at intervals between the time of injection of the typhoid vaccine and the development of fever showed no essential change.

During the chill, in the case of malaria as well as typhoid, the EEG showed evidence of marked muscular activity. Shivering, and particularly chattering of the teeth, was associated with rapid spikes varying in frequency between 15 and 20 per second (Fig. 1). To some extent both the shivering and the spike potentials could be controlled voluntarily by the patient.

There was a grossly detectable alteration in the EEG during the rise in temperature in 22 of the 23 patients, and the alteration was almost always progressive. The nature of the alteration in the majority of records could be summarized as follows (Figs. 1 and 2): (1) An increase in the irregularity of the pattern. (2) An increase in the number of slow or delta waves. (3) An increase in the voltage of the potentials. A few of the fever tracings contained both rapid and slow activity, but with the latter dominating the record.

The rise in temperature was associated with progressive loss of the characteristics of the patient's basic electrogram, and the pattern at high temperatures (104° to 105° F.) was utterly different from that at the control temperature. With the decline of fever there was a gradual resumption of the original characteristics. When the patient was entirely afebrile, the electrical pattern was again similar to that of the prefebrile period.

There were variations in the magnitude of changes during fever which were to a large extent in accordance with the severity of the paroxysm—that is, the rapidity of the rise of fever and its final height. The more rapid the rise and the greater the final elevation of temperature, the more marked the changes in the EEG.

In addition, the more severe the clinical picture of the disease, the more marked were the changes during the fever.

During fever, the EEG showed considerable individual variation in the amount of delta activity. In some cases the delta activity appeared at random throughout the record, in other cases the delta activity was

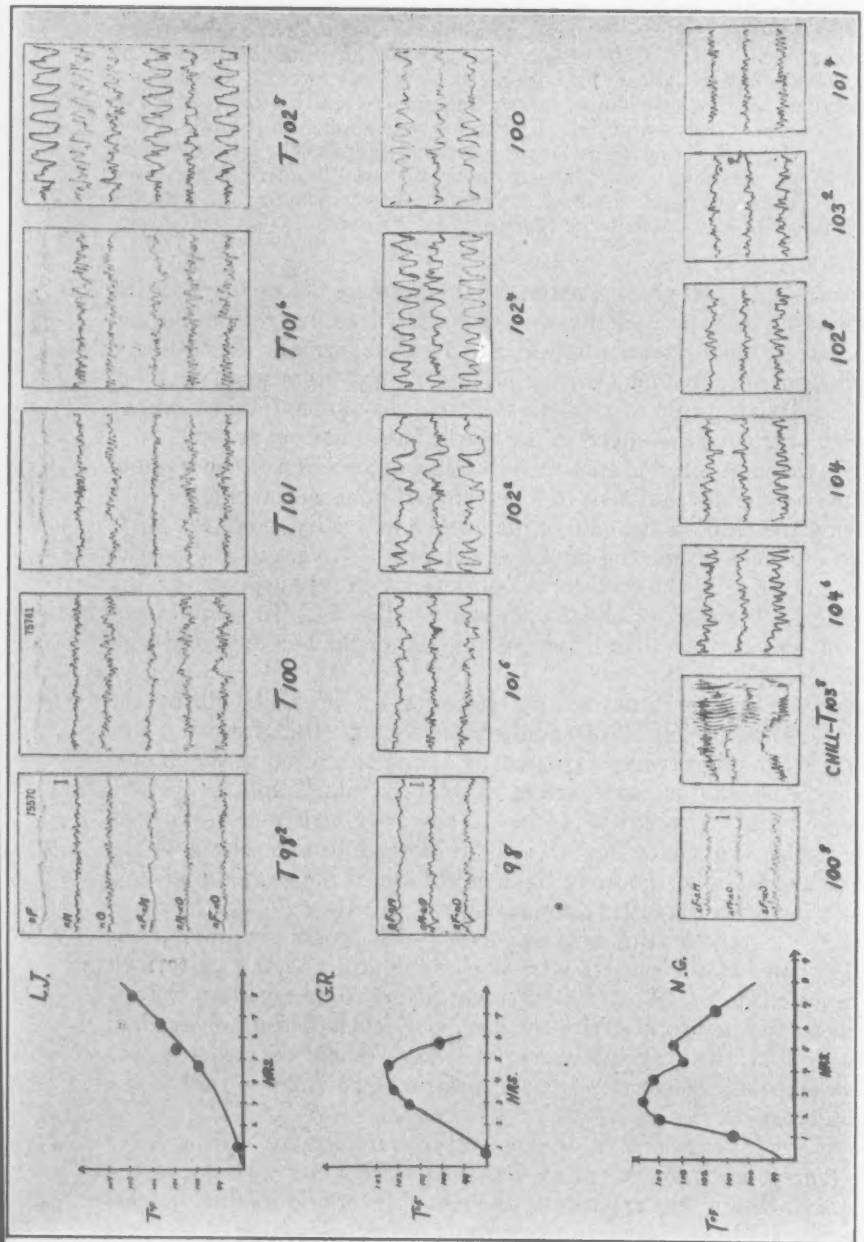

FIG. 1.—*EEG changes during fever.* Tracings during fever in 3 patients with neurosyphilis. The dots on the graph at the left represent points on the fever curve at which the tracings to the right were taken. All leads are from the right hemisphere. The records of *L.J.* and *G.R.* are of 3 seconds duration and are both monopolar and bipolar. The records of *N.G.* are of 2 seconds duration and are bipolar only. The upright calibration line in the first tracing of each series represents 50 m.v. Note that changes in the EEG parallel the rise and fall of temperature. Patient *L.J.* showed progressive slowing of the waves and increase of voltage with the rise of temperature until at 102.8° F. bursts of high voltage 2 to 3 per second slow cycles appeared, many with spike and wave configuration. Patient *G.R.* showed 2 to 3 per second high voltage delta activity at 102.4° F. with considerable slow activity remaining even at 100° F. Patient *N.G.* shows rapid spikes due to the chill at 103.8° F. with relatively little slowing of the cycles even at 104.2° F.

continuous, and in still other cases the delta activity was "organized" into bursts of high voltage slow cycles, 2 to 3 per second (Fig. 1). The episodic slow rhythm during fever could not have been anticipated from the control tracing, although the latter might have been abnormal (Fig. 1). Some of the records during fever suggested strongly the type of activity seen in epilepsy and allied disorders.

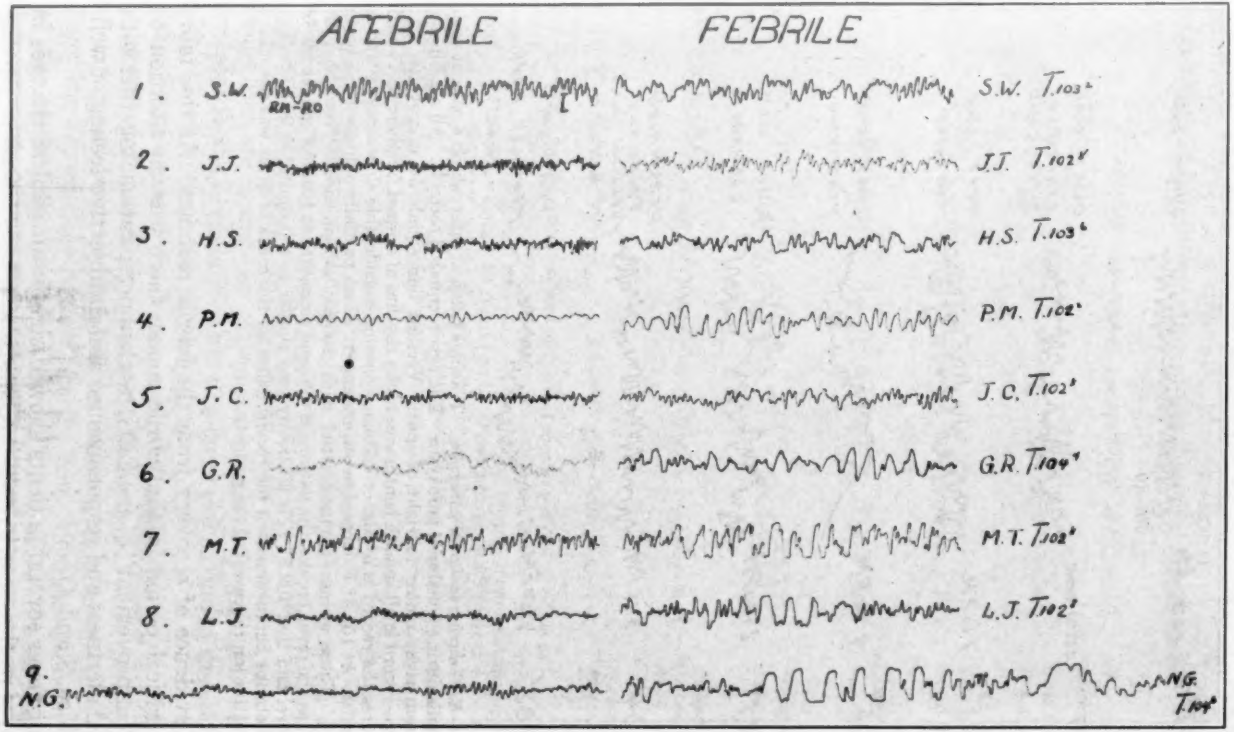

FIG. 2.—Nine varieties of brain-wave patterns in patients with neurosyphilis and the corresponding patterns during fever. The patterns of Nos. 4, 5, 6, 7, 8, and 9, during fever showed "episodes" of slow waves in groups. The tracings are all bipolar from the right motor to right occipital area. The length of the upright line in the upper left tracing is equal to 50 microvolts. All tracings are of 5 seconds duration except No. 9, which is of 7 seconds duration.

There was considerable individual variation in the rate of return of the EEG to normal during the decline of fever. Comparison of records at a given temperature during the decline of fever and during the rise of fever revealed that the two were not identical. In some patients there was a relatively abrupt return to the basic characteristics of the EEG in the early defervescence of fever, and this was associated with

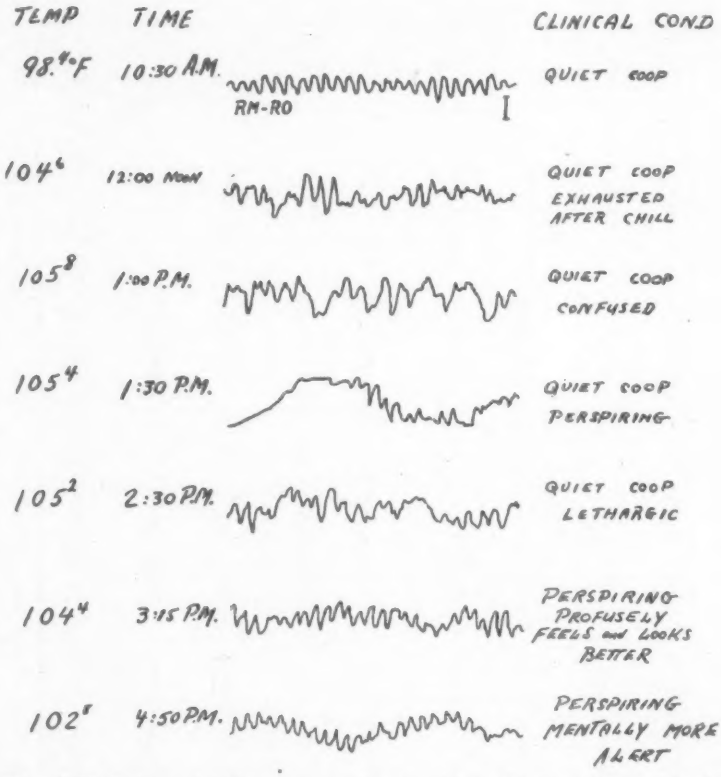

FIG. 3.—*EEG during malarial paroxysm.* Tracings taken at intervals on a patient with neurosyphilis during a malarial paroxysm. Each strip equals 3 seconds. All are bipolar records from right motor to right occiput. Vertical line equals 50 microvolts. At 98.4° F, the record is all smooth continuous alpha rhythm of normal frequency. At high temperatures the record is of higher voltage, contains considerable slow activity and is very irregular. At 105.4° F. large slow swings appear which partially obliterate the brain potentials. These swings are associated with marked perspiration. Note that at 104.4° F., as the fever breaks, the pattern is different from that at 104.6° F. on the rise of temperature, and that 102.8° F. it is already very similar to the control at 98.4° F. The relatively abrupt improvement of the record following the break of fever was associated with subjective improvement of the patient.

clinical evidence of recovery from the febrile reaction. At this more or less critical period in the febrile course there was, in addition to abrupt "improvement" of the EEG, marked perspiration, together with increased alertness and responsiveness and a subjective feeling of well-being (Figs. 3 and 4).

During fever several patients showed significant clinical changes in the form of restlessness, irritability, listlessness, and confusion. Apathy

and listlessness followed regularly after marked exhausting rigor. Confusion appeared particularly when the temperature was very high in patients whose orientation previously was not clear. These patients, by and large, showed the most changes in their EEG tracings.

Discussion. Knowledge regarding the changes of the brain potentials in various conditions is of importance in understanding the physiology of the brain and in improving the interpretation of the EEG in clinical conditions. Fever is a dramatic phenomenon inviting interest and frequently yielding information of fundamental significance.

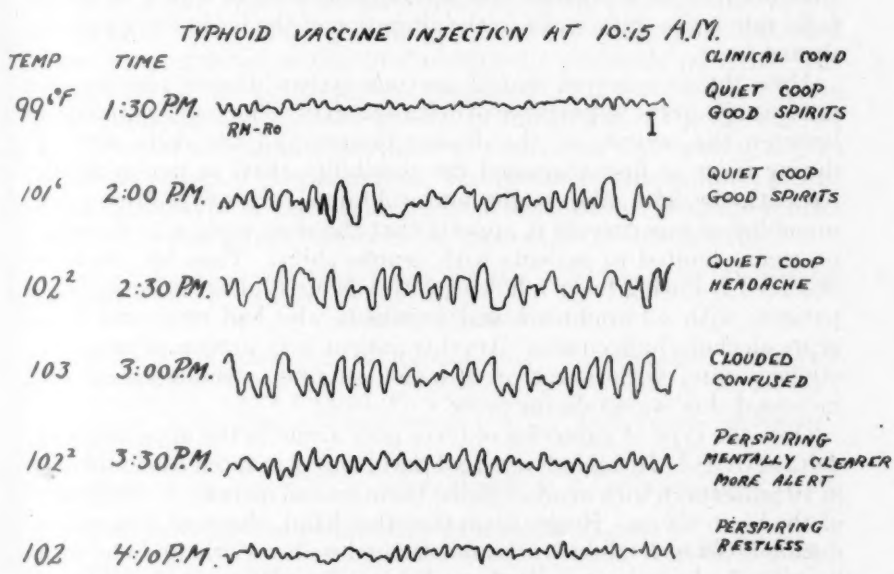

FIG. 4.—*EEG during fever produced by typhoid vaccine.* Tracing taken at intervals on a patient with neurosyphilis during a paroxysm following intravenous typhoid vaccine injection. Each strip equals 5 seconds. All are bipolar records from right motor to right occiput. Vertical line equals 50 microvolts. During fever, high voltage slow activity dominates. At 102.2° F. on the downgrade of fever, the pattern is much more like the control (99.6° F.) than at 102.2° F. on the upgrade of fever. Relatively abrupt improvement in the brain waves during early defervescence was associated in this case with clinical improvement.

The main feature of the records in this study is an increase in the slow or delta activity during fever. The higher voltage found is that usually to be expected in association with slow activity, and the irregularities are mainly an expression of mixed frequencies. In the fever records, the irregularities are to a large extent due to the addition of slow waves to the basic pattern.

What is the cause of the delta activity? Is it the fever? To be sure, the amount of delta activity is in general correlated with the height of the temperature; but the fact that at a given temperature in the rise of fever the record does not necessarily show identical delta activity as at the same temperature in the fall of fever, indicates that the temperature *per se* is not the whole explanation.

That the increased metabolism in fever is not the sole reason for the alteration in brain potentials is suggested by the reports of increased frequency of brain waves in patients who as a result of thyroxin or dinitrophenol administration develop a rise in basal metabolic rate.[8] Also, it is reported that patients with hyperthyroidism generally have increased wave frequency, while patients with myxedema generally show decreased wave frequency.[7] Although the records obtained during fever show predominantly decreased wave frequency or slow wave activity, occasionally there is admixture of cycles more rapid than normal. It is possible that several influences, of which the metabolic rate is one, play a rôle in the alteration of the brain-wave pattern during fever.

Does the presence of central nervous system disease play an important rôle in the appearance of delta activity? The rough correlation between the severity of the disease process and the delta activity during fever at first suggested the possibility that, in non-syphilitic patients, the delta effect might not be obtained. However, from a few unpublished experiments it appears that the slow wave activity is by no means limited to patients with neurosyphilis. Thus far, we have observed it during fever following intravenous typhoid injection in 2 patients with schizophrenia and 1 patient who had recovered from acute alcoholic hallucinosis. Another patient with pyrexia of unknown etiology (and with negative tests for syphilis) demonstrated also increased slow waves during fever.

Does the type of induction of fever play a rôle in the appearance of delta activity? Hoagland[5] reported that in fever induced by diathermy in 10 patients (6 with neurosyphilis) there was an increase in frequency of the brain waves. Berger,[2,3] on the other hand, observed slow waves during fever in 2 tabetic cases, one treated with malaria and one with "pyrifer." In our cases, both typhoid and malaria acted similarly; that is, increased delta activity was associated with fever. These data suggest that the method of induction is possibly to be taken as a significant factor. We should point out, however, that until a great deal more is known about the phenomenon of fever and its effect on the brain potentials, it is unwise to speak of the effects observed as caused by the fever. Alteration of temperature from any cause is only one manifestation of many disturbances of body physiology.

One striking feature of the records is that the delta activity may be sporadic, continuous, or organized into bursts of 2 to 3 per second slow cycles. Several runs of very suggestive spike and wave activity (L.J., Fig. 2) were observed in a patient without a history of seizures. Records with sporadic or continuous delta are seen frequently in cases with intracranial pathology, and records with episodic slow activity are seen frequently in epilepsy and allied disorders. This raises interesting problems: (1) the possibility that fever is a method of eliciting abnormal activity which does not occur in the basic pattern; and (2) that the abnormal activity is related to the epileptic predisposition of the patient or to intracranial disease. Patients with neurosyphilis frequently develop convulsions during the course of

their illness, and fever may precipitate convulsions in non-luetic children and some adults. On the other hand, if correlations with epilepsy and intracranial pathology are not established, this finding will serve to emphasize the lack of specificity of special wave forms as indicators of specific diseases.

Summary. Twenty-three patients with neurosyphilis were subjected to 54 bouts of fever induced by intravenous typhoid vaccine injection and therapeutic malaria, and EEGs were taken before and at intervals during the fever. As the temperature rose there was a gradual increase in the amount of delta activity in the voltage and in the irregularity of the brain potentials, and as the temperature subsided there was a gradual return to the subject's prefebrile pattern. The magnitude of the changes were correlated with the severity of the fever paroxysm and with the severity of the disease. The delta activity appeared as sporadic slow waves, continuous slow waves, and as organized bursts of slow activity. The factors of temperature, rate of metabolism, type of disease, and type of induction of fever are considered as possible causal factors in the production of slow activity.

We are indebted to Miss Marie Healey and Mrs. Janet Lavery for able technical assistance.

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THE USE OF EQUINE GONADOTROPIN IN MALE INFERTILITY*

An Analysis of 127 Patients

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The treatment of male infertility, which began with the earliest realization of the husband's responsibility in a barren marriage, was given its greatest impetus with the discovery of the pituitary gonadal relationship. This discovery led to the introduction of human pregnancy urine and of menopausal urine as potential spermatokinetic agents. The results obtained with the use of these products were not satisfactory. The extract of pregnant mare serum (equine gonadotropin) was then introduced and it, in turn, has received wide therapeutic trial. Although this substance was found to possess unusual

* The author is indebted to Dr. David R. Meranze, Director of Laboratories of the Mount Sinai Hospital, for his aid in interpreting the histologic sections presented herein.

spermatokinetic qualities in the experimental animal, the paucity of clinical reports reflects the lack of good results in the human.

Our own clinical experience with equine gonadotropin has been equally disappointing. Although the results are somewhat better than those obtained with the products previously employed, the stimulative properties of even these gonadotropins do not measure up to experimental expectations. It is our purpose in this report to analyze the results of treatment with equine gonadotropin, to examine critically the lesions associated with the semen deficiencies and to deduce therefrom the reasons for failure of treatment. Is the gonadotropin which was potent experimentally, ineffective in the human; or are we dealing with lesions of the human seminiferous tubules which are different from those found or induced in the experimental animal? Does the administered gonadotropin have insufficient spermatokinetic qualities clinically, or is the lesion of the testis of such a character that the germinative epithelium is no longer capable of responding to stimulation?

This report is based on material gathered over a period of nearly 4 years. The conclusions as to the ineffectiveness of equine gonadotrophin are based on an analysis of 230 consecutive patients treated with this substance. However, 103 of these patients either received other treatment in addition to the gonadotropin, or were insufficiently observed or inadequately treated. The final analysis is therefore based on a review of the results in 127 patients with faulty spermatogenesis treated with equine gonadotropin only. The preliminary studies done on the 127 patients included not only a physical examination and the usual laboratory tests, but a testicular biopsy as well. Urine studies for the determination of androgen and gonadotropin content were done only in the few instances in which they were especially indicated. The determinations were inconclusive and are not included in this report. The equine gonadotropin* was administered intravenously. The dose employed in 119 patients was 400 I.U.† administered 3 times weekly for a period of from 3 to 6 months. Seven patients were given 800 I.U. and 1 patient 2000 I.U. 3 times weekly.

Observations in 127 Patients. The results of treatment with equine gonadotropin in the 127 patients are summarized in Table 1. Of the 127 men treated, 12 were "cured," 22 were "improved" and 93 remained unchanged. The terms "cured" and "improved" refer to semen changes only. As a criterion of cure, a *total* count of at least 200 million spermatozoa was arbitrarily chosen.‡ Any increase of the spermatozoan population which did not reach this figure was considered as representing only improvement. Small increases of the sperm count, such as increases from an initial 2 million to a post-therapeutic 3 million, were considered as variations having no relation

* Anteron, generously supplied by the Schering Corporation.

† I.U., International unit. An international unit is "the specific gonadotropic activity of 0.25 mg. (250 gammas) of the standard preparation in possession of the Health Organization of the League of Nations." One rat unit (Cartland-Nelson) equals 15 I.U.

‡ This figure is to be compared with a total of 350 million spermatozoa, generally accepted as average normal.

to treatment and were therefore classified as unchanged. Ultimate pregnancy in the wife was not accepted as a criterion. Patients with large increases in the sperm count were classified as cures even though pregnancy did not occur. Conversely, one with a constantly low sperm count was classified as unchanged even though his wife became pregnant during the course of treatment.

No attempt is made to divide the semen deficiencies into the usual clinical groups, *viz.*, azoöspermia and oligozoöspermia, since it is our contention that the two have similar etiologies and that the difference between them is merely one of degree. Similarly, in this short résumé, the individual sperm counts are not listed in detail. It is to be noted, however, that better results were obtained in patients who had the higher sperm counts at the beginning of treatment. This observation is quite significant and will be dealt with below.

The Scope of Testicular Biopsy. Up to the present time, failures of treatment have been generally attributed to inadequacy of the administered gonadotropin. The nature of the lesion involving the seminiferous tubules (and accounting for the reduced spermatozoan population) has received little attention. No one has up to now seriously considered the possibility that a very large proportion of these lesions do not result from gonadotropin deficiency and can therefore not be repaired by gonadotropin administration. Generally the pre-therapeutic classification has consisted of a differentiation between oligozoöspermia and azoöspermia. Patients with non-obstructive azoospermia have generally been given a poor prognosis, whereas those with oligozoöspermia have been encouraged to take treatment on the supposition that the few spermatozoa in the ejaculate indicated healthy but incompletely matured seminiferous tubules, each of which had failed to yield its maximum quota of spermatozoa.

Fortunately, the lesions affecting the seminiferous tubules are subject to close scrutiny. This is accomplished by means of testicular biopsy. In 1940,[1] we reported the use of testicular biopsy in the diagnosis of male infertility. More recently,[2] we described a variety of testicular lesions found on biopsy in instances of faulty spermatogenesis. A satisfactory classification of these lesions is still not available. Many more histologic sections require careful study before an acceptable and workable classification is made. For the present, the following clinico-pathologic groupings, based on the severity and the relative reversibility of the lesions, are presented because of their usefulness in prognosis. Of the 4 groups listed below, only Group 3 contains underfunctioning seminiferous tubules which may be expected to regenerate under favorable conditions.

1. *Complete Atrophy.* The seminiferous tubules are lined by a single layer of undifferentiated cells. The basement membrane is often wrinkled from shrinkage and may or may not be thickened. The semen contains no spermatozoa (Fig. 2).

2. *Severe Degenerative Changes.* Atrophy is incomplete. The seminiferous tubules are lined with 2 or 3 layers of germinative epithelium. Cellular vacuolization is widespread. Maturation is nowhere present. The basement membrane of the tubule may be normal in appearance but very often is thickened

and fibrotic. This fibrosis may be so extensive that the ring it forms is thicker than the tubule itself. In many instances, round cell infiltration is present as evidence of inflammation. The semen contains no spermatozoa (Fig. 3).

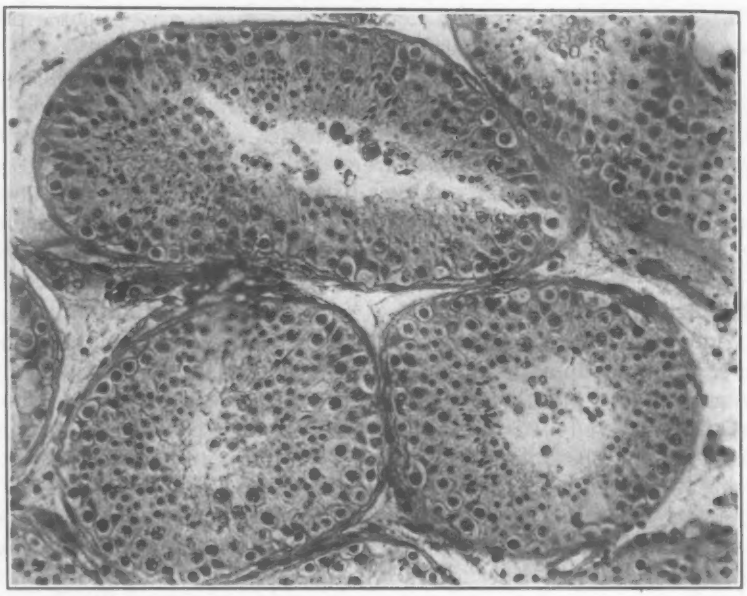

FIG. 1.—Normal, showing highly cellular, regularly organized elements. (X 250.)

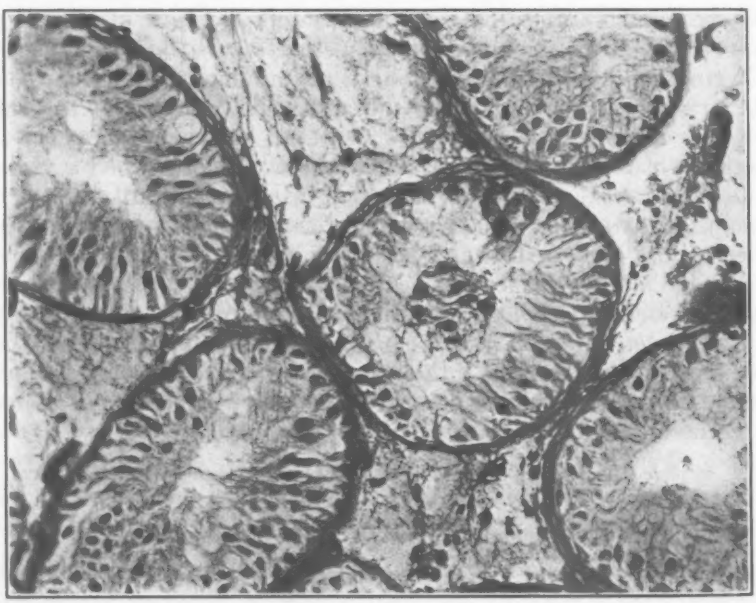

FIG. 2.—Complete atrophy. Only a single layer of undifferentiated cells is present in most tubules. There is slight peritubular thickening. (X 250.)

3. *Moderate Degenerative Changes.* The pathologic process is less advanced than in group 2. The seminiferous tubules contain more cellular layers. Evidence of maturation is now present though not widespread. Cellular

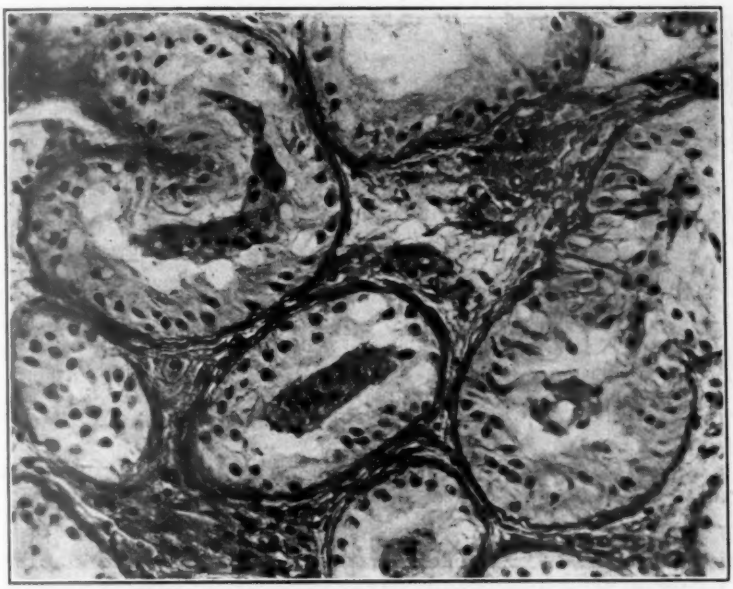

FIG. 3.—Advanced degeneration. The tubules contain 2 or 3 layers of seminiferous epithelium. No evidence of maturation. (X 250.)

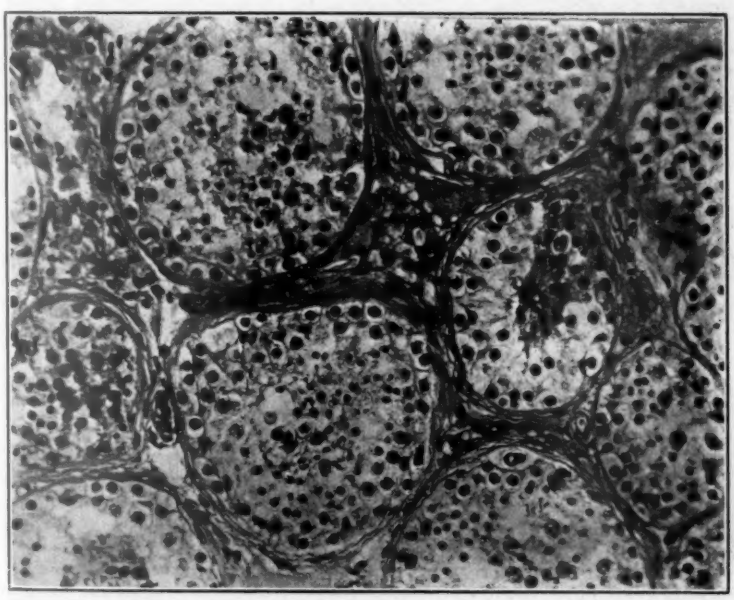

FIG. 4.—Moderate degeneration. Note disorganization of cellular elements even in the highly cellular tubules. Compare with Figure 1. Two of the tubules reveal some maturation. Sperm count 8,200,000 per cc. (X 250.)

vacuolization is common. A great many of the tubules have only 1 or 2 layers of cells, their lumina being filled with cellular débris. The basement membrane is usually normal, but peritubular fibrosis may be present. The semen con-

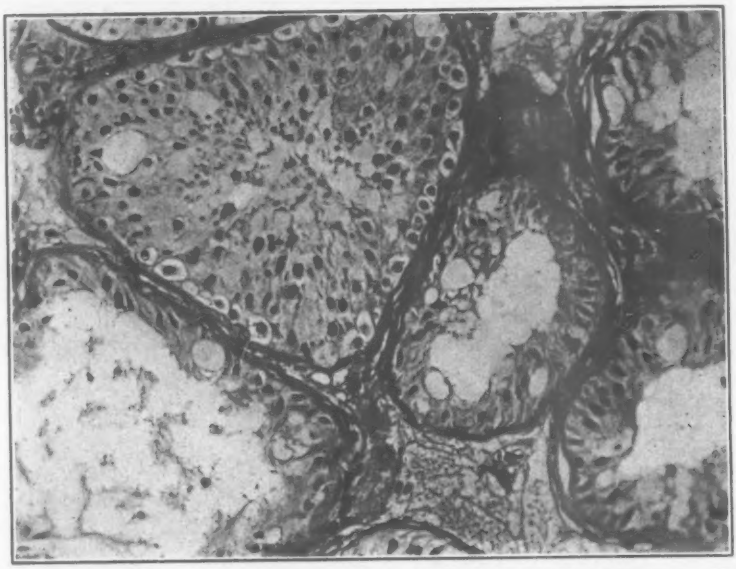

FIG. 5.—Islands of relatively normal tubules surrounded by atrophic ones. (X 250.)

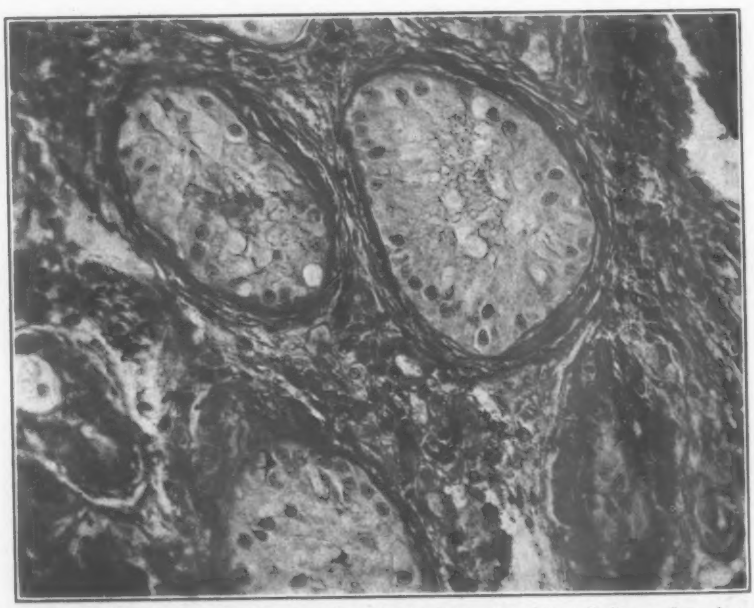

FIG. 6.—Failure of development—characterized by atrophic tubules and an increase in interstitial tissue—chiefly of connective tissue elements (cells with dark staining elongated nuclei). Note relative sparcity of cells of Leydig. (X 250.)

tains some spermatozoa, the number depending on the prevalence of matured tubules (Fig. 4).

4. *Combinations of Groups 1, 2 and 3.* The healthier tissue is usually arranged in small islands which are surrounded by tubules displaying the various degenerative phases already described. The islands may contain healthy, matured tubules or even these may show evidence of underdevelopment or degeneration. The surrounding tissue reveals the more advanced tissue changes. Spermatozoa are found in the ejaculate only if there are matured tubules in the islands (Fig. 5).

As already stated, this classification is presented merely to list the lesions according to their severity, thus attaching to them a prognostic significance. In addition, there are observed, at all levels of severity, certain pathologic features which appear to have an etiologic significance. These are:

1. In instances of atrophy or severe degeneration the size of the tubules may be normal or reduced. It is assumed that in these cases the size of the tubules is an index of the stage at which development ceased and degeneration set in. Thus, small atrophic tubules indicate failure of development, whereas atrophic tubules of normal size point to degenerative changes which set in after development was more or less advanced.

2. At any of the levels of degeneration, the presence of peritubular fibrosis is indicative of a long-standing pathologic process. If accompanied by round cell infiltration it is definite evidence of a previous inflammation, even in the absence of a clinical history of orchitis.

3. The character and quantity of the interstitial tissue is significant. There is apparently an increase in the amount of normal interstitial tissue (but not necessarily in the interstitial cells of Leydig) in instances of clear-cut endocrine underdevelopment. This is a more or less constant feature and is observed even when the seminiferous tubules are normal in size. It may serve to differentiate between an endocrine and non-endocrine etiology (Fig. 6).

This classification would be of little practical importance if the correlation between the biopsy and semen findings were constant But that is not the case. Tubules which yield no spermatozoa may be completely atrophied (Group 1) and irreparable, or they may reveal only moderate degenerative changes (Group 3) which are reversible. An individual with a very low sperm count may possess underdeveloped tubules most of which can be stimulated to growth under favorable conditions, or he may have small islands of mature tubules interspersed among tubules showing extensive atrophy (Group 4). These mature tubules are already functioning at full capacity and attempts at further stimulation are useless. Another patient with a moderately reduced sperm count may possess a large number of irreparably degenerated seminiferous tubules surrounding normally functioning ones (Group 4), or he may reveal healthy tubules which are somewhat immature and require only adequate stimulation by gonadotropins (Group 3). Furthermore, testes whose function has been impaired by a previous inflammation, as evidenced by peritubular fibrosis and round

cell infiltration, are not likely to respond to any type of stimulation, not even to the administration of gonadotropins of adequate potency. Finally, one may find an oligozoöspermia in an individual whose biopsy reveals an abundance of normally functioning tubules. Under such circumstances, the reduction in the sperm count is associated with evidence of seminal vesicular infection and impaired drainage through the ejaculatory ducts. In such cases, treatment should be directed toward elimination of the infection rather than to administration of gonadotropins. With the introduction of sulfonamide therapy, the percentage of "cures" in this group has been greatly increased. The results of this form of therapy are soon to be reported in a separate communication.

TABLE 1.—RESULTS OF TREATMENT WITH EQUINE GONADOTROPIN

No. of patients	127
"Cured"	12 (9.3%)
"Improved"	22 (17%)
Unchanged	93 (73.7%)

Thus, these studies serve to emphasize the importance of testicular biopsy not only in evaluating the degree of damage to the seminiferous tubules but also in determining the correct indication for gonadotropin therapy. Moreover, a second biopsy following a given period of treatment with gonadotropins yields definite information relative to the efficacy of the administered product, especially in those instances in which reëxamination of the semen fails to show any improvement.

Evaluation of Gonadotropin Therapy. The results of treatment with equine gonadotropin are obviously poor. One must keep in mind, however, that this is an analysis of consecutive unselected patients and that it is not therefore a fair estimate of the value of equine gonadotropin when it is administered only to patients in whom it is indicated. An explanation for the lack of response to the gonadotropins is found in the data uncovered by testicular biopsy in the 93 patients in whom repeated semen examination revealed no improvement. In 48 of these patients the biopsies preliminary to treatment revealed any one of the irreparable lesions illustrated above, the most prominent of which was peritubular fibrosis. This was very often associated with round cell infiltration, indicating an inflammatory origin. These lesions were obviously not produced by an endocrine deficiency and could therefore not be repaired by endocrine administration. After a trial period of treatment with gonadotropins, biopsies were repeated in 4 of these patients. Examination of the histologic sections failed to reveal any growth of the germinative epithelium.

The remaining 45 patients revealed lesions which were potentially reversible. These lesions could conceivably have been produced by gonadotropin insufficiency, although even some of them may have had other etiologic backgrounds. Of these 45 patients, testicular biopsies were repeated after a test period of treatment in 15. Of these 15, 11

revealed increased growth of the germinative epithelium of the tubule, even though the semen picture remained unchanged (Table 2).

TABLE 2.—ANALYSIS OF FAILURES. CORRELATIONS OF RESULTS OF TREATMENT WITH BIOPSY FINDINGS

	Histologically irreparable lesions	Histologically reparable lesions
Number of patients	48 (52%)	45 (48%)
Number of patients with semen improvement	0	0
Number of biopsies after treatment	4	15
Number of patients with improved histologic picture after treatment	0	11 (73%)

However, this epithelial growth seemed to be limited to a multiplication of the younger cell forms. Cell division occurred, but maturation did not follow. The failure to produce actual maturation of the germinative epithelium may have resulted either from the fact that the administered gonadotropin lacked a maturation fraction or that it was not sufficiently potent and should have been administered in larger dosage. The answer remains just as obscure when the data of the 12 "cured" patients are examined. With 2 exceptions the lowest *total* sperm count before treatment was 50 million. Testicular biopsies in these patients uniformly revealed a good number of actively functioning seminiferous tubules. Even those tubules which were not normal contained several layers of differentiated epithelial cells which would conceivably require little stimulation for maturation. The widespread atrophy, noted in some of the advanced oligozoöspermias, indicating a poor prognosis, was absent.

Summary and Conclusions. 1. Results in a series of 127 *unselected* cases of male infertility treated with equine gonadotropin are unsatisfactory, although the substance appears to have therapeutic value in selected cases.

2. The various histologic pictures of the seminiferous tubules found on testicular biopsy in infertile men are herein described. Detailed study of the histologic sections of the patients who improved and of those who failed to respond to treatment shows a remarkable consistency in the ability to prognosticate the outcome from testicular biopsy.

3. The percentage of patients who reveal irreparable lesions of the seminiferous tubules is surprisingly high (52%). It is useless to employ gonadotropin therapy in these individuals.

4. Of the patients with faulty spermatogenesis 48% revealed seminiferous tubules which could conceivably regenerate. The failure to obtain an equally large percentage of "cures" is either the result of insufficient potency of the administered gonadotropin of the lack of a maturation fraction therein.

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ANALYSIS OF RESULTS OBTAINED WITH SMALL DOSES OF GOLD SALTS IN THE TREATMENT OF RHEUMATOID ARTHRITIS*

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In 1929, Forestier[1] reported favorable results with injections of gold salts in the treatment of arthritis. Many reports have appeared since then and the consensus of opinion is that the method has a definite place in the treatment of rheumatoid arthritis even though there may be toxic reactions which may even be fatal. The mechanism underlying the beneficial effect and the toxic reactions is unknown, the dosage and method of treatment still being given on an empirical basis. The number and severity of toxic reactions which occur with the commonly recommended dosage and the unscientific basis for this dosage made it desirable to investigate the subject further.

This study was begun in 1940 and was given further impetus by Hartung's[4] findings that the bacteriostatic property of the sera of patients who had received 150 mg. of gold salts was similar to that of patients who had received 900 mg. in the same period of time (6 weeks). Later, Freyberg[2-3] published the results of his study on the concentration of gold in the plasma and its elimination in urine, feces, etc. He concluded that: (1) With increasing doses of gold, there was a general tendency toward an increase in the blood gold level and in its urinary excretion, followed by a leveling-off, even though greater retention may have been accruing. (2) When injected weekly, the amount of gold eliminated did not exceed 25% of that injected at any one time. (3) Plasma values were highest 1 hour after the injection, but remained above normal for 24 hours, varying with the amount of gold injected. (4) The higher the dose, the greater the urinary excretion of gold. (5) Gold was found in the blood and urine as long as 9 to 12 months after injections, the length of time being approximately proportional to the size of the weekly dose. After a weekly dose of 12.5 mg., gold was found in the blood and urine for 1 month; after 25 mg. it was found for 3 months; and after 50 mg. for 6 to 10 months. (6) Toxic reactions were much more frequent in

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patients who received large weekly injections, the severity usually being proportionate to the amount of gold injected. (7) With smaller doses, the same therapeutic results were obtained as with the conventional larger doses.

The studies of these 2 investigators further strengthened our belief that the conventional dosage of gold salts was unsuitable.

Materials and Methods. Gold thioglucose,* which contains 50% of gold, was given intramuscularly to 100 patients with rheumatoid arthritis who had high sedimentation rates. The interval and dose varied from time to time to determine the minimal effective dosage.

Dosage.† From preliminary experiments it appeared that small doses would give satisfactory results in rheumatoid arthritis. The tentative schedule adopted was 5 mg. intramuscularly twice a week for 3 weeks; 10 mg. twice a week for 3 weeks; and then 25 mg. once a week. If toxic symptoms did not develop after 3 weeks of the latter dose, they rarely appeared subsequently. Most of the patients were given 25 mg. a week throughout the series, but in a few cases that showed no improvement after 4 weeks, the dose was increased by 5 mg. every 2 weeks until improvement occurred or until 50 mg. a week was reached. For example, if improvement occurred on 35 mg. a week, the dose was not increased further. However, if the improvement did not continue the dose was again increased but never above 50 mg. We did not give a definite course of injections but continued gold salts indefinitely, or for at least 12 months. In this way we were able to prevent the relapses that so frequently occur with the standardized course method.

In some instances, the initial dose was even less than 5 mg. a week. In patients with severe rheumatoid arthritis with very high sedimentation rates, moderate to severe anemia, marked loss of weight, insomnia, and all the signs of active infection, or in older people, the dose was only 2 or 3 mg. twice a week for the first 4 weeks, then 5 mg. twice a week for 4 weeks, 10 mg. twice a week for 4 weeks, and finally 25 mg. a week, as tolerated. However, a fixed dosage schedule is undesirable and every patient must be studied individually.

Toxicity. Toxic symptoms following this therapy fell into the following groups: cutaneous (localized dermatitis, dermatitis exfoliativa, urticaria, etc.), mucus membrane involvement (ulcers in mouth and throat, gastritis, enteritis, vaginitis, etc.), hematologic (anemia, purpura, agranulocytosis, etc.), renal and hepatic. With the small doses employed in this study, 42% developed toxic symptoms, 50% of which occurred before the patients had received 100 mg. of this gold preparation and 86% before they had received 200 mg. If toxic symptoms did not appear by that time they seldom occurred subsequently, and larger doses, up to 50 mg. per week, were usually tolerated without unfavorable effect. Patients receiving the smaller doses quickly recovered from toxic symptoms, the severity and duration being proportionate to the size of the weekly dose and the total amount of gold injected. This confirms the findings of Freyberg.[2-3]

As small a total dose as 20 to 30 mg. occasionally was followed by toxic symptoms. However, they usually were mild and disappeared after a few weeks. Four patients developed toxic symptoms of doubtful classification. One developed edema of both legs which disappeared

* Solganal-B Oleosum, the material used in this study, was furnished gratis by Schering Corporation.

† All dosages given in this paper are in terms of gold thioglucose rather than in terms of gold.

after the treatment was discontinued, but returned when the injections were resumed. The urinalyses were negative, and we were unable to account for the effect. Another who was quite ill developed severe hiccoughs, apparently secondary to hepatitis, which persisted for 3 weeks. A third patient had a severe, prolonged headache not

TABLE 1.—THE RELATIONSHIP OF TOXIC REACTIONS TO THE DOSE OF GOLD THIOGLUCOSE

Type of reaction	Total dose (mg.)	Average weekly dose (mg.)	Interval (weeks)	Duration of toxic symptoms (weeks)
Cutaneous (17):				
Dermatitis exfoliativa	655	25	26	13
	730	24.33	30	10
	200	20	10	7
Localized dermatitis	70	20	3	4
	130	16	8	5
	80	11	7	4
	60	8.5	7	5
	110	9	12	6
	100	10	10	3
	80	8	10	2
Scarlatiniform rash	80	10	8	2
	90	10	9	2
Maculo-papular eruptions	40	7	6	2
	70	8	9	3
Urticaria	25	6	4	2
	80	10	8	3
Angioneurotic edema	20	10	2	2
Mucous membrane involvement (11):				
Pharyngitis	20	5	4	2
Vaginitis	145	14.5	10	4
	130	16	8	5
Stomatitis	130	16	8	3
	40	7	6	1
	20	5	4	1
	80	11	7	2
	90	10	9	4
	120	10	12	5
Gastritis	200	20	10	6
Colitis	200	20	10	8
Liver involvement (2):				
Hepatitis	200	20	10	6
Hepatitis with hiccoughs	220	20	11	5
Kidneys (5):				
Hematuria	190	9.5	20	4
	210	21	10	5
Albuminuria	80	11	7	5
	100	12	8	7
	150	15	10	8
Hematologic (2):				
Reduction in platelet count	20	7	3	2
	80	20	4	3
Central nervous system involvement (1):				
Encephalitis with vertigo	240	24	10	5
Type undetermined (4):				
Headache	135	11	12	3
	160	20	8	5
Vertigo	130	13	10	4
Edema of legs	80	11	7	3

relieved by the usual remedies, which was thought to have been the result of gold toxicity. Two who had vertigo were confined to bed for 1 and 2 weeks. They developed moderate anemia, complained of drowsiness, anorexia and nausea, and generally appeared to be quite ill. The symptoms could only be accounted for on the basis of gold encephalitis.

If large doses had been given in these 4 cases, the symptoms undoubtedly would have been more prolonged and more serious, and a fatality probably would have occurred in the patient with the more severe vertigo, drowsiness, etc. All other patients in the series, except those with dermatitis exfoliativa, recovered rapidly and did not appear to be seriously ill at any time.

When any toxic or doubtful symptoms appeared, the gold therapy was discontinued immediately. When the drug was omitted as soon as toxic symptoms first appeared, they usually disappeared in a few weeks. The use of gold was then resumed cautiously.

Forty-two per cent of the patients developed some signs of toxicity. This is higher than others reported but it includes even those with mildest toxic symptoms.

Some patients that received the gold treatment for more than a year developed toxic symptoms several times and treatment was discontinued temporarily each time they appeared. If the same dosage was used, toxic symptoms occurred as a rule when the same total amount had been injected, provided the period of rest was sufficient to allow elimination of the gold previously given. If the rest period was insufficient to eliminate it, then toxic symptoms would occur before the same total amount of the drug had been injected.

In analyzing the toxic symptoms that resulted from gold treatment in this study, we observed that low doses produced urticaria, angioneurotic edema, maculo-papular eruptions and reduction in the platelet count; medium doses, scarlatiniform rash, localized dermatitis, vaginitis, stomatitis, albuminuria, etc.; and large doses produced dermatitis exfoliativa, gastritis, colitis, hepatitis, hiccoughs and encephalitis with vertigo.

Results. Over 100 patients were treated with the dosage described. The results compare favorably with those obtained by conventionally larger doses. Fifty-three per cent of the patients were markedly improved with almost complete remission of symptoms: 21% were definitely improved and 12% showed slight improvement, a total of 86% that showed some degree of improvement. Table 2 illustrates 10 cases picked at random from the group considered as having shown marked improvement.

One of the criteria for improvement in arthritis is a reduction in the erythrocyte sedimentation rate. In almost every patient classed as improved there was a reduction in the sedimentation rate, but occasionally a patient that showed subjective and objective signs of improvement, such as increased motion, relief from pain, swelling, stiffness, etc., showed no reduction in the sedimentation rate. There was

definite improvement in a number of instances where toxic reactions developed, even though the total amount of gold salts administered was small.

TABLE 2.—TEN CASES, PICKED AT RANDOM, OF THE 57 THAT SHOWED MARKED IMPROVEMENT AFTER TREATMENT WITH GOLD THIOGLUCOSE

Sex	Aver. wkly. dose (mg.)	Total dose (mg.)	Interval (Wks.)	R.B.C. (million)		W.B.C.		Platelet count		Sed. rate (mm.)	
				Before	After	Before	After	Before	After	Before	After
F	19	494	26	3.77	3.06	7,350	10,200	240,000	190,000	64	15
F	18	292	14	3.70	3.65	6,300	8,250	341,000	205,000	62	12
M	20	400	20	5.21	4.45	12,650	20,000	175,000	282,000	82	14
M	28	392	14	5.10	4.02	10,000	9,650	260,000	275,000	105	45
M	21	630	30	4.48	4.03	8,400	9,850	208,000	197,000	28	4
F	25	400	16	4.20	3.99	9,700	8,400	200,000	256,000	36	6
F	18	360	20	3.88	3.99	8,400	5,700	218,000	208,000	85	25
F	25	600	24	3.54	4.33	6,300	9,400	219,000	230,000	110	35
F	22	440	20	4.43	4.00	9,400	10,000	190,000	206,000	84	20
F	29	435	15	5.10	4.60	11,200	6,100	250,000	190,000	74	14

The improvement noted was usually so definite both to the physician and the patient that there was no doubt as to the results even though the doses employed were far smaller than conventional ones. There was the additional advantage that the dangers associated with large doses were avoided.

Discussion. The results obtained with small doses of gold thioglucose warrant further study of the subject. The use of these small doses enables the physician to detect patients who are hypersensitive to the gold preparation before large total doses have been given, prevents the accumulation of large amounts, and eliminates most instances of serious toxicity which are the constant worry of physicians administering the drug. We did not have any instances of serious toxicity with the small doses used. However, use of even these small doses is not entirely devoid of danger and the physician should be constantly alert for any symptoms of toxicity. Toxic symptoms occurred frequently in the present series but close observation and immediate omission of gold therapy as soon as they appeared usually resulted in only mild and temporary reactions, probably because a smaller amount of gold had been stored in the system and less time was required to eliminate it.

If, as Freyberg showed, less than 25% of the weekly dose of gold is eliminated during the period of treatment, the question arises as to whether it is necessary to store the remaining 75% which appears to be the cause of prolonged toxic symptoms. Our experience indicates that this is unnecessary.

Investigators of gold therapy are well aware of the relapses that occur when the drug is omitted. In the earlier cases of the present series, severe relapses were sometimes observed 1 month after gold therapy had been discontinued in patients who had been obtaining excellent results. With the small dose method proposed in this paper, gold salts therapy can safely be continued for a long time. This method was followed in the latter part of this study and the number and severity of relapses were greatly reduced.

The results obtained by us in 100 cases are comparable with those obtained with conventional doses but there were fewer serious toxic reactions. With conventional doses the toxicity is so great that the method frequently is abandoned. It certainly is dangerous in the hands of inexperienced investigators.

Conclusions. 1. It is possible to detect patients who are sensitive to gold therapy in the treatment of rheumatoid arthritis by using much smaller doses than are usually employed.

2. By increasing the dose only as it is tolerated, the number and severity of toxic reactions are markedly reduced.

3. The favorable results (86%) obtained with these small doses are comparable with those reported by others with much larger doses.

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PROGRESS
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OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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VASOMOTOR RHINITIS

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Vasomotor rhinitis is a term currently employed to describe a triad of nasal symptoms: sneezing, nasal obstruction, and a watery or mucoid type of discharge. Occasionally, there may be present such associated symptoms as itching and loss of the sense of smell. The terms vasomotor rhinitis and hyperesthetic rhinitis, according to the more recent literature, are just as fashionable as allergic rhinitis and nasal allergy, this despite the fact that at one time the older literature spoke of paroxysmal rhinorrhea, turgescent rhinorrhea, nasal hydrorrhea, perennial hay fever, nasal neurosis, nervous coryza, spasmodic coryza, or intermittent neurotic catarrh.

The symptoms of vasomotor rhinitis vary considerably in different individuals both as to degree and duration. Any one of the nasal symptoms may dominate the clinical picture and any one, in turn, may be submerged. Sneezing occurs in paroxysms and is accompanied by a watery, alkaline, irritating type of nasal discharge. In the presence of an associated secondary infection, the nasal discharge may become mucopurulent. Itching of the nose may precede sneezing or be disassociated from it. Not infrequently, itching involves other structures—the eyes, mouth, pharynx, and occasionally the larynx. Nasal obstruction is usually pronounced and incurs considerable discomfort. The nasal mucous membranes usually are pale and appear swollen and "water-logged." More rarely, the mucous membrane will show a pinkish color or even slight congestion and redness.

There has been a pronounced tendency among allergists to regard the vast majority of cases of vasomotor rhinitis as being based on an allergic origin. This point of view has gained many adherents in rhinologic circles. Nevertheless, some rhinologists, in the light of negative skin tests and by the apparent absence of the usual inhalant, protein and food factors, consider numerous cases of vasomotor rhinitis to be of non-allergic origin.

Allergic Aspects. Since there is some vagueness in the term "vasomotor rhinitis," Urbach[30] has proposed a specific classification. He offers the term "rhinopathy" to cover all the conditions known as rhinitis and, in turn, differentiates this as allergic rhinopathy when the cause is specific

allergy, and pathergic rhinopathy when the cause is a non-specific hypersensitivity. Allergens to be considered under allergic rhinopathy are: exogenous substances, or those exerting an influence on the nasal mucous membrane; foods or drugs taken by mouth; and endogenous substances, such as products of the endocrine glands, of metabolism or of bacteria in the intestines. Pathergic rhinopathy can be the result of an underlying general or nasal infection, of a local irritation, of psychic disturbances, and also of a non-specific broadening of a hypersensitivity which was formerly specifically allergic. Included under pathergic rhinopathy are the paroxysmal attacks of sneezing with subsequent swelling of the nasal mucous membrane, following exposure to sudden changes in temperature; attacks of sneezing attributable to hypersensitivity to cold or heat; and sneezing brought on by looking into bright sunlight. On the basis of 74 cases, Urbach found that in 54 individuals the symptoms were caused by a variety of non-specific factors; in about two-thirds of the remaining cases, they were specifically allergic; in one-sixth, they were due to endocrine disturbances, and in one-sixth to intestinal disturbances. He believes there is no standard method of treatment. Whenever possible, each patient should be treated etiologically. Operations are usually without lasting effect, and occasionally they are even harmful. Treatment of allergic rhinopathy depends on elimination or desensitization, and treatment of pathergic rhinopathy consists in an attempt to lower the hypersensitivity of the nasal mucous membrane and simultaneously to increase the patient's resistance.

In a discussion of the allergic aspect of vasomotor rhinitis, Gelfand[12] states that three guides to successful management are complete history, clinical observation and exhaustive tests. A history should include the patient's own description of home and occupational environment, of home, business and social contacts, of cosmetics and clothing used, hobbies, sports, and other activities. The food intake should be checked by food diary or elimination diet. Intradermal tests should cover all possible materials to which the patient may be allergic. After employment of all possible irritants and in various concentrations, the patient can be considered cutaneously insensitive to that particular material only if he fails to react to the strongest extract. It is believed necessary to use every kind of allergen to which the patient has shown sensitivity, even when his contacts with some have been casual or infrequent. Intensive therapy consists of rapidly working up to a dose by increasing the frequency of treatments to twice or three times a week and then continuing with the maximum dose at short intervals. Analysis of 52 cases of perennial vasomotor rhinitis revealed an allergic origin in 89%. Most patients showed multiple sensitivities, but, with few exceptions, vasomotor rhinitis was the sole clinical manifestation; only a few had hay fever, asthma and urticaria. Dust sensitivity was present in 95%, and sensitivity to occupational allergens other than dust was demonstrated in 41%. These allergens included animal fur, dyes and chemicals used by furriers, feathers, wool, cotton, kapok, wheat, rye, pyrethrum, and odor of paint. Housewives showed sensitivity to dust, orris root, feathers, tobacco, perfumes, and animal epithelium. Treatment consisted of injecting or avoiding all specific allergens that could be demonstrated; in some patients both measures were utilized. Of the 52 patients, 24 improved, 6 were relieved, 10 had fair results, and 12 were unimproved or referred elsewhere. Some investigators[1,6a,b,16] have identified molds, yeasts, rusts and smuts, insect emanations, and other inhalants as etiologic factors in perennial vasomotor

rhinitis. Ingested drugs and chemicals have also been implicated. Eyermann[3] studied 181 patients with vasomotor rhinitis due to ingested foods and found that the foods most frequently eaten were the ones most often responsible for sensitization. He advised that the influence of foods and inhalants be investigated before resorting to injections of pollen. Sternberg and Sorrell[27] refer to specific occupations in which vasomotor rhinitis and asthma occur when the potentially sensitive subject comes in direct contact with certain antigens to which he becomes specifically sensitized through direct exposure. They state that such individuals may give positive cutaneous reactions which are not due to chemicals or drugs. After studying 45 patients with vasomotor rhinitis, Shahan[26] advances the following recommendations: removal of offensive inhalants and foods from the patient's environment; employment of immunization or hypersensitization when necessary; provision of a balanced diet after offensive foods have been eliminated; removal of foci of infection; palliative medical treatment; and change of environment, when possible. Cooke[2] also claims that the treatment of vasomotor rhinitis consists of recognition and avoidance of the cause, and immunization, or the attempt to develop a protective antibody. Some proteins in ragweed pollen cause marked skin reactions but stimulate the protective mechanism only slightly. If after injection there are symptoms of a general reaction, 0.5 cc. epinephrine (1 to 1000) should be given hypodermically and the tourniquet used promptly. Little can be done with drugs to allay the symptoms of hay fever, and cocaine sprays should never be employed since the habit is easily formed. A 1% ephedrine spray may give temporary relief but should not be employed over a long period of time or too frequently.

In a discussion of the significance of the nose in allergic states, Frackelton[10] declares that an allergic state may be prolonged as a result of the locking up of residual allergens within the sinuses or being trapped beneath the turbinates. Swelling of these bodies, resulting in prolonged contact with the septum, may cause the allergen to penetrate to the submucosa and produce sensitivity of the underlying periosteum and bone. He believes that post-nasal irrigation with isotonic solution of sodium chloride enables the fluid to reach the nasal spaces not accessible to anterior irrigation, with removal of residual allergens. The same principle applies to the maxillary sinus, which should be irrigated after an attack of nasal allergy or after the hay fever season. Frackelton also recommends "allergic surgery," whenever indicated, so as to relieve the tissues from pressure due to anatomic or pathologic changes. By "allergic surgery" is meant the correction of a deviated septum, removal of spurs, trimming the hyperplastic turbinates, or amputation of the anterior end of the middle turbinate. It is claimed that the freeing of the intranasal structures from the possibility of prolonged contact of mucous surfaces prevents intramucosal penetration, and when this is done in conjunction with the irrigation the possibility of absorption of allergens, as well as of secondary infective agents, is prevented and the remote effects so often seen in allergic patients are guarded against. King and King[19] write that despite every measure adopted and every effort put forth by the allergist and the rhinologist, there are patients whose disease is refractory to treatment. They review and analyze their experiences with 9 patients, all having the same nasal symptoms, their reactions to cutaneous tests being negative, and their disease refractory to treatment. The following recommendations are advanced: determine the skin reactions as soon as possible; control the environment; try diets strictly free from milk and wheat over extended

periods. If there is no response, bacterial allergy should be considered. Cultures of the nose and sinuses can be made and the administration of stock vaccines begun. A trial should be made of the various empiric remedies such as histaminase, thyroid and estrogens, with chemotherapy given in selected cases. The authors believe that good results will come in the vast majority of cases only through careful, painstaking effort with each individual patient.

Riccitelli[24] discusses the influence of season and climate in relationship to the various manifestations of nasal allergy. He asserts that cosmic and meteorologic conditions have a deep influence on physiobiologic processes through the changes in temperature, variations in the amount of actinic rays, and the degree of electricity in the air. All these factors are more or less rhythmic in their changes, and therefore it may be expected that allergic persons will react correspondingly. Spring is the season when hyperergic reactions are most manifest and at this time the inorganic phosphorus and calcium contents of the blood are lowest. Therefore, a study of mineral metabolism is important. Luscher[22] attributes the allergic tendency to a hereditary hypersensitivity of the vegetative nervous system and a disturbance in the neurovegetative balance whereby the autonomic nervous apparatus affects the local reaction in tissues to various irritants. He feels that in cases of such hyperirritability there frequently may be an additional psychic factor which enhances the reaction. He cites the various stigmas so commonly existing in such cases and agrees that the presence of eosinophilia in the secretions, tissues and blood is a valuable diagnostic sign. Jaffe[18] reports his observations on vasomotor rhinitis in the tropics and states that in some cases an allergic origin has been demonstrated while in others such an origin is questionable. The prognosis is rarely serious, but a complete cure is difficult to obtain. One hundred and thirty patients with vasomotor rhinitis were treated in the republic of Honduras in Central America. Vasomotor rhinitis was found to be quite common in this climate. There was a great deal of dust, especially in the cities, and it was felt that this was a factor. The patients were treated by cauterization of the mucous membrane with a concentrated solution of trichloracetic acid. The author warns against unnecessary operations, and suggests methods of conservative therapy which have been found to be satisfactory. Glover[14] finds that an allergic nose must sooner or later be subject to infection because of the impairment of ventilation and ciliary action caused by the allergic swelling of the tissues. It is therefore important to treat the infection actively as well as to employ measures capable of overcoming the allergic state. Farmer and Kaufman[5] have employed histamine in the treatment of perennial and seasonal allergic rhinitis. The histamine was given by subcutaneous injection, and the injections were increased each time by 50% if well tolerated. Among 41 cases of perennial rhinitis the result was reported good in 25, fair in 10, and poor in 6. Successful results were obtained in 26 of 33 patients with perennial vasomotor rhinitis by Gant, Savignac and Hochwald[11] after each individual dosage of histamine (1 to 1000) dilution had been established.

Non-allergic Aspects. According to Mohun,[23] vasomotor rhinitis and associated conditions have a definite incidence during pregnancy. He describes the cases of 8 pregnant women who experienced a severe degree of nasal blocking and congestion during pregnancy; in the non-pregnant state none of these women had ever experienced such difficulty. Twelve other pregnant women experienced severe nasal blockage, but these

patients had a history of previous transient attacks of hay fever and nasal blocking in the non-pregnant state. In 9 patients with purulent sinusitis the infection was more protracted and the mucous membrane more swollen than is usually encountered. They showed no response to customary therapy, but the condition cleared quickly after delivery in all instances. From both a theoretic and clinical standpoint, allergy did not seem to be the predominant etiologic factor. The incidence of vasomotor rhinitis during pregnancy appears to be parallel and to be caused by the amount of estrogen produced in the body. Characteristically, the condition disappears spontaneously after delivery. Fowler[8] describes a case of unilateral vasomotor rhinitis due to interference with the cervical sympathetic system. This case suggests to him that experimental surgery might uncover the fundamental mechanism of vasomotor rhinitis. If one can produce vasomotor rhinitis at will, one should be a long way toward understanding allergic diseases more thoroughly. Animal surgery may localize the part of the sympathetic or the parasympathetic nervous system which needs to be attacked for prevention or cure. Citing the report of the Asthma Research Council after 5 years of investigation, Stovin[28] states that the reasons for dissatisfaction with the therapy of vasomotor rhinitis are to be found in too much dependence on desensitization and not enough on body chemistry. There may be an unrecognized imbalance, for example, between the cations of sodium and those of potassium. In contrast to the diminishing effectiveness of epinephrine is the sustained and often increasing effectiveness of supportive therapy. Stovin believes that the use of diet rich in protein and acid ash and low in sodium chloride, combined with the administration of potassium iodide and bicarbonate, has proved effective. A similar diet, as for bronchial asthma, combined with the administration of the chloride salt of potassium has given excellent results in the general treatment of vasomotor rhinitis.

Nasal Medication. According to Houser,[17] anti-allergic therapy often fails to secure satisfactory results, although there are enough successes, in full or in part, to justify the continuation of allergic studies and treatment. There are certain measures worth trying in the attempt to relieve individuals who in spite of all efforts remain wretched and partly incapacitated with blocked and discharging noses. The measures most likely to secure results all have as their goal a desensitization of a considerable portion of the nasal mucous membrane. Electrocoagulation, the galvanocautery, the injections of solutions of alcohol, quinine and urea, and sodium morrhuate, the application of a chromic acid bead or a 30% solution of phenol and trichloracetic acid have been reported as measures improving or freeing the patient of symptoms for a period of time varying from a few weeks to many months. In spite of the possibility of securing results by these procedures, the nasal mucous membrane should not be subjected to these relatively harsh measures, Houser states, unless anti-allergic therapy has failed. The use of a watery paste of resorcinol has been suggested by Lewy.[21]

The administration of sclerosing preparations into the submucosa has a long list of ardent devotees. In general, these agents include hypertonic saline solution, glycerin, sodium salicylate, quinine lactate, alcohol, quinine and urea hydrochloride, a 5% solution of calcium sodium lactate, and sodium morrhuate. Vail[31] has favored the injection of alcohol into the inferior turbinate and septum, while Ruskin[25] and Walsh[32] have injected alcohol into the nasal ganglion. Fishof[7] and Thacker and Hauser[29] have reported that vasomotor rhinitis is relieved by submucosal injections of a

5% solution of sodium morrhuate. They believe that the use of this agent does not impair the physiology of the nasal mucous membrane and that, clinically, no deleterious effects are detected. There is comparatively little pain or discomfort after the injection, and most patients require but 1 or 2 injections of 0.5 cc. of the 5% sodium morrhuate solution in one or both inferior turbinates. Associated symptoms, such as headache, neuralgia of the sphenopalatine ganglion, and post-nasal dripping were markedly diminished or cured. In the experience of Fox,[9] the use of sodium psylliate solution (Sylnasol) in more than 200 cases of chronic vasomotor rhinitis by injection is highly successful.

The status of zinc ionization (iontophoresis) with respect to vasomotor rhinitis still remains a subject affording considerable difference of opinion between the allergist and the rhinologist and between one rhinologist and another. Those who have had much experience with the procedure in select cases still advocate its use; those who dispute its value are increasingly antagonistic to its employment. While a good part of the controversy settles on the question of how much damage actually is done to the nasal mucous membrane following zinc ionization, it has been pointed out that electrocautery, certain drugs and chemicals, Roentgen rays and radium often produce much greater damage to the nasal mucous membrane than does ionization. Kuhn and Linton[20] discuss their limited experiences with the use of ionization. In a few cases where there was no improvement with hyposensitization and in cases where the symptoms of seasonal allergy were well advanced at the first examination, ionization has been found satisfactory in about 50% of the cases. The authors did not encounter the destructive and atrophic changes attributed by some writers to ionization. In nasal cases in which no allergen could be found, and the patient is proved to have a low basal metabolic rate, small doses of thyroid have relieved the nasal symptoms completely. Glas[13] employed histamine iontophoresis in increasing doses, beginning with a solution of 1 to 2000 and reported excellent results in some instances.

The use of liquid nasal medicaments for the relief of nasal discomfort in vasomotor rhinitis is indicated, even though the relief is often temporary; for even a measure of relief is welcomed by distressed and distracted patients. At one time solutions of epinephrine administered by nasal spray or medicine dropper had considerable vogue. With the advent of ephedrine and synthetic ephedrine-like preparations, the employment of epinephrine has, for the most part, fallen by the wayside, for when the effects of the latter wear off nasal symptoms may return in a more exaggerated form. Epinephrine, therefore, is not a suitable agent for local application in the nasal cavity. Ephedrine in 1% physiologic saline, or one of the synthetic preparations, is more effective and is generally used for relief. Occasionally, undesirable side effects are produced as a result of absorption through the mucous membrane, but as a general rule this does not take place.

Hansel[15a,b] asserts that in the field of allergy the cytologic content of nasal and sinus secretions may be considered an approximate index of the pathologic processes occurring in the tissues, and that the cytologic observations give important diagnostic information. In allergy, it is particularly significant that when the pH of these secretions falls on the acid side, there is a complete disappearance of the eosinophiles. When the pH returns to the alkaline side, there is a return of the eosinophiles. Fabricant[4] tested the pH of nasal secretions *in situ* in cases of allergic rhinitis and found these secretions to be alkaline during the active stages

of the allergic rhinitis. The nasal pH descended to the neutral point and then to a slightly acid status when clinical improvement was felt by the patient. Whenever the symptoms became aggravated, a return to an alkaline status was detected. From the point of view of applied nasal therapeutics, Fabricant suggests that during the more active stages of allergic rhinitis the employment of a nasal vasoconstrictor which can lower the abnormal alkaline nasal status to a normal, slightly acid status—a pH level between approximately 5.5 and 6.5—may perform a valuable function.

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DERMATOLOGY AND SYPHILOLOGY

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THE "LUPUS ERYTHEMATOSUS" CONCEPT: AN ATTEMPT AT INTEGRATION

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THE manner in which the synthetic creation of entities from symptomatology may occasionally leave the specialist out on a limb etiologically is well illustrated by the complex misnamed "lupus erythematosus." A syndrome of multiform character, with lesions ranging from the insignificant local cutaneous to the promptly fatal polystructurally systemic;

originally described by the dermatologist Hebra[34] as part of the seborrheic-infective complex and now in fair way to be swallowed by the internist as a disease of the vascular system, lupus erythematosus has at best only a distant relation to the cutaneous tuberculous processes suggested by its conventional name. The literature reveals a variegated patchwork of opinion as to cause, slowly working into a pattern that will combine a central etiologic conception with a wide range of peripheral manifestations. This review aims to outline such a conception.

When the dermatologist wishes to hypothesize on variegated peripheral manifestations, he turns to the vascular mechanism as providing the most immediately eligible network for dissemination; and when local particulate noxæ, like microörganisms in lesions, cannot be found, he tends these days to turn to infection allergy in its various expressions, including the Sanarelli-Shwartzman[73,78] phenomenon to explain the clinical and histologic characteristics of the dermatosis. In dermatologic terminology as applied to lupus erythematosus this means an effort to combine the multiform erythema syndromes with the "id" concept in such a way as to account for the multiplicity of clinical manifestations that appear as variants upon the erythematous lupus base. So wide is the range of variation in symptoms and course that the theory must account at one sweep for a life-time of benign follicular keratitic patches below the malar prominences, in 1 case; the livid purple erythema of the Kaposi[40] facial eruption in another; and the occasionally almost lesionless skin of the young woman dying with nephritis and pneumonia of acute disseminate lupus erythematosus in a third.[1,5,7b,10,11,14,22,23,25,26,29,31,38,39,41b,41c,41d,54,55,56,59,64,69,70,71,74,81,84,86,90.]

Nomenclature and Classification. Ambrosetti[1] has collected most of the classification that has developed about the clinical picture from Hebra's[24] "seborrhea congestiva" to Kerl's amplification of Ehrmann and Falkenstein's[21] classification (of which Urbach and Thomas's[86] is a modification), which includes 6 types based largely on the acuteness and dissemination of the process. It seems best to stress here the localized discoid and the disseminated multiform types of lesions, as the two main categories, from which sub-varieties of acute and subacute discoid and localized and disseminate discoid can be made up, as well as acute and subacute multiform varieties. The discoid and the multiform types may interweave, disclosing 1 or 2 discoid chronic lesions in the scalp of a patient dying of acute multiform or disseminate erythematous lupus; or a discoid chronic localized type of the disease of years' standing suddenly passing over into an acute multiform disseminate type with rapidly fatal outcome. This confusing polyphase character, heterogeneity of symptoms, and interweaving of types can, it seems to us, best be resolved by setting the picture over against two groups of dermatologic lesions now well known to be among the expressions of infection-allergy; the cutaneous *follicular* "ids" (trichophytids, tuberculids, mycotids, staphylococcids, streptococcids, etc.) and the multiform erythemas as expressions of vascular injury and allergy.

Application of the "Id" Conception. The elementary lesion of chronic discoid erythematous lupus is a follicular inflammation with atrophy. It differs essentially from the follicular lesions of other types of "ids" such as trichophytids, follicular tuberculids (lichen scrofulosorum) only in that the plug or "propf" is more conspicuous than the papule, and in the sequela of atrophy, which rarely follows the involution of other follicular "ids." That the histologic picture presented by the follicular lesions of erythematous lupus is that of allergic inflammation is supported by such

studies as those of Baccaredda,[4] who regards the cellular picture as comparable to that found in tuberculids and "microbids." The homologies with allergic inflammation are also stressed by Rost.[72] Fibrinoid degeneration of the collagen, which may lead to the atrophy and scar in discoid lupus erythematosus, were experimentally produced by Gerlach[28] and Klinge[45] in another field—that of rheumatic fever—and interpreted as accompaniments of allergic (hyperergic) inflammation. In fairness one must, however, recognize that there is not as yet a general acceptance of colloid degeneration as a sign of allergic reaction. Klemperer, Pollack and Baehr[44] have in fact vigorously opposed it in their description of "diffuse collagen disease" as a pathogenic entity.

As a theoretical basis for classifying the follicular lesion of discoid erythematous lupus as an "id" or allergic reaction to an infection, the allergic inflammation concept of Rost and others has, then, it would seem, some merit. Using such an interpretation, one might link together through the occurrence of similar "allergic" histologic change in other than skin tissues and in vessel walls, renal glomeruli, and so forth, the chronic discoid form of erythematous lupus and its clinical team-mate, acute disseminate erythematous lupus. The range of infection-allergic inflammatory disease might even be made to include the Libman-Sacks[47,48] syndrome, the sclerodermatomyositis complex, and periarteritis nodosa (Banks[5]).

If the discoid type of erythematous lupus be then thought of as a follicular "id" or infection-allergic reaction in the skin proper, a variety of scattered considerations becomes to some extent reconcilable with clinical experience. The folliculo-allergic reaction as it might be designated, in discoid lupus erythematosus, commonly occurs over the most light-exposed parts of the face. Light is a well-recognized physical allergen. A variety of other influences may still further enhance the allergic effect. The sites of involvement are, for example, also those of the flush area of the face and head as well as those of light exposure; and a rich congestive vascular background, as in the Meltzer-Auer[3,57] conception of local allergic response, contributes markedly to allergic reaction. Thus circulating allergens brought from distant points to a congested area might exacerbate a discoid process in lupus erythematosus. Emotion as a vasodilator might then contribute to persistence and relapse in lupus erythematosus as observed by Callaway and Stokes.[13] Circulating light sensitizers (porphyrins) would be brought in increasing amounts to congested areas specially bombarded by light rays.[8,51,85a] Light and cold as physical allergens known to produce exacerbations of erythematous lupus would be acting conceivably not only on their own allergic merits but also as powerful local insults to stimulate the injurious effect of an underlying infection-allergy. The commonly observed clinical association of discoid erythematous lupus of the face with the seborrheic-infective process in the scalp gives a clue to a possible source of infection-allergy which may apply also in the more obscure and complex picture of the Senear-Usher[90] syndrome. Discoid lupus erythematosus can be hypothetically accounted for then as follicular (seborrheic) infection plus allergic reaction to that infection (yeasts and staphylococci).

The dissemination of a discoid or follicular erythematous lupus (a lupo-erythematid?) with the appearance of desquamative patches with follicular atrophy over other parts of the body, is simply an extension of the follicular "id" beyond its conventional locus, under conditions affecting the general allergic state of the individual. His allergic base can be broadened by

one or another influence, bringing on such exacerbation and generalization. It may even be by the administration of a sulfonamide, which in accord with Barber's[6] conception causes exacerbation and dissemination by flaring a concealed systemic focus of infection (liberation of streptococcal toxin), thus modifying the local follicular and the general skin allergic substrate. To none of these "id"-like processes, which are allergic manifestations in the skin itself, need grave prognostic significance usually attach—the benign prognosis of the disseminating discoid type of the disease is well known. *On the other hand,* in the hypersusceptible person—the infection-allergic type of individual, let us say—the epidermo-allergic or folliculo-allergic type of reaction that underlies the chronic discoid process may at a suitable provocation pass over (though only occasionally) into the field of vasculo-allergic manifestations and assume the far graver characteristics of the so-called acute disseminating type of the disease (*cf.* Fox, 1943[24]).

The Vasculo-allergic Manifestations in Lupus Erythematosus. As the discoid type of lesion is expressive of local cutaneous infection-allergy of the follicular inflammatory type with atrophy, so the acute disseminate type is the clinical type of lupus erythematosus with multiform disseminated cutaneous and systemic lesions resulting from allergic inflammation of the vascular system. In order to conceive of acute disseminate lupus erythematosus as an erythema multiforme, it is necessary to expand one's clinical conception of the multiform erythemas to a degree not always acceptable to dermatologists.[41a] The multiform erythemas are, however, generally conceded to include acute and chronic types of which erythema figuratum perstans, erythema elevatum diutinum, sarcoid-like infiltrations and even granuloma annulare are well recognized or extreme and controversial variants. In the chronic types of erythema multiforme the experienced observer will find examples of the atrophic changes of erythematous lupus side by side with the edematous wheals, the purple plaques, and circinate and gyrate figures of erythema multiforme. The "deep" types of indurative erythematous lupus are approaches to the multiform erythema group of erythematous lupus manifestations. The Kaposi[40] *erysipelas perstans faciei* is morphologically a chronic erythema multiforme early recognized as one of the forms of disseminate erythematous lupus. The pellagroid type of lesion, the acute edema and exfoliation, and even focal necrosis of the skin of the face representing acute light injury in a rapidly fatal erythematous lupus is obviously a different process from the local follicular "id" of the discoid lesions but it is nonetheless an allergic response. Such reactions represent, perhaps, localized acute vascular injury, occurring when a circulating photosensitizing allergen meets the effective wave length of actinic energy. When we come to the more extensive processes, the multiform nodose and plaque types of lesions, the infiltrations of skin and subcutaneous tissue,[7b,38] the infiltrative livedo and Bazin-like tuberculoid lesions that the infection-allergic nature and vascular distribution of the process or agent is also strongly suggested. For this group of widely disseminated multiform manifestations in the erythematous lupus complex we would suggest the designation "acute or chronic vasculo-allergic type," using "chronic" rather than "acute" in certain cases, in deference to the view of such observers as Rose and Pillsbury[71] that disseminate erythematous lupus is a long-standing disease of the vascular system before it comes to acute exacerbative manifestations in the skin.

The vasculo-allergic type of "lupus erythematosus" then, may be preponderantly local and cutaneous in its manifestations, or preponder-

antly systemic (fever, lymphadenopathy, leukopenia, absolute or relative, with or without thrombocytopenia, and with demonstrable vascular lesions of the eyes, kidney and endocardium). It may be acute or chronic, or both. It may be combined with follicular "id" lesions of discoid type and distribution, or not. The systemic vasculo-allergic lesions may come to notice first and dominate the picture to exitus. But we suspect as dermatologists that the insistence of certain authors and clinicians that a complete absence of skin lesions is not uncommon, may be due to inadequate search for or non-recognition of the cutaneous ones. Certainly we believe that a diagnosis of disseminate erythematous lupus sine erythematous lupus, in the broad interpretation of multiform erythematous lesions, must be made with caution.

The Infection-Allergic Mechanism in Lupus Erythematosus. Such emphasis on allergy of infection, cutaneous (follicular or epidermal) and vascular, as capable of welding into a comprehensible unity the disparate and confusing interplay of lesions included among the captions "discoid" and "disseminate," "acute," "subacute" and "chronic," now requires an accounting. It must be confessed that the clinical case for infection allergy is not massively *pro*, though there is also little *con*. The importance of infection allergy in the lupus erythematosus complex is supported by (*a*) the extreme, even fatal reactivity of disseminate types, to tuberculotoxin; (*b*) the recognized danger of stirring up a focus of infection (especially dental) in disseminate cases; (*c*) most recently by experiences with the sulfonamides, which appear to help some cases by subduing an infection focus, or, in reverse, make others worse as in Barber's observation [6] by activating or stirring up a focal infection

As to the nature of the infection to which allergy develops or exists, no absolute decision can be had at this time. There is sharp disagreement on the presence of tuberculous infection in individuals coming to autopsy with erythematous lupus. Many authors are still aligned on the tuberculous side, while the more recent trend is toward the non-tuberculous nature of lupus erythematosus. The data on this subject in the literature from 1871 to 1942 is tabulated by Ambrosetti.[1] A similar controversy has persisted over the years, it will be recalled, in regard to erythema nodosum, which has finally been stilled by the compromise that in some countries it is often tuberculous, in others rarely so. In other words, there is a tuberculously-backgrounded *form* of the non-specific erythema nodosum picture. Why can there not be such in lupus erythematosus disseminatus? Streptococcal infection has on the whole made a much better case for itself. Among the authors supporting the view that bacterid (streptococcal) foci (toxemia) are etiologically important in the background of the disease complex are Keil,[41a] L. W. Shaffer[77] and Barber.[6] It is, however, more or less accepted that the organisms obtained from the blood stream in occasional cases (tubercle bacillus, *B. alkaligenes fecalis*, *Staph. aureus*, pneumococcus, *Strep. anhemolyticus* and *hemolyticus*, *Strep. viridans*) are coincidental,[41a,70] or are terminal bacterial invasion.[47] A possible virus (ultramicroscopic agent) etiology has been suggested by Belote.[10] No experimental work as yet has accomplished the reproduction of the clinical picture of erythematous lupus in any of its forms, in animals. On the allergy side of the problem clinically, there may be cited the extreme, even rapidly fatal reactivity to certain infective agents or toxins above mentioned. The occurrence of leukopenia as an almost unvarying accompaniment of the disseminative and acute types of erythematous lupus, is perhaps suggestive of an allergic

assault on the bone marrow, though a number of observations attest the normality of the bone marrow in some of the cases in which it was studied. Thus far, the subject has been inadequately examined from the standpoint of the allergic background, familial and personal, in either the acute or the chronic types. As an allergy of infection, it is of course possible that the yield of such inquiry would be small when related to allergic reactivity in general. The *photosensitivity phenomena* in lupus erythematosus furnish some of the strongest evidence for the allergic factor, yet photosensitivity seems to play no part in many cases and the incidence is not statistically overwhelming in countries or at seasons in which sunlight is particularly abundant. That porphyrins are merely incidentally present in the stools, blood or urine is contended by Goeckerman, Osterberg and Sheard.[32] The more recent work tending to establish certain types of intestinal organisms as responsible for the formation of light-sensitizing porphyrins, however, suggests a mechanism by which a bacterial focus (the intestinal tract is rarely investigated as such in studies of focal infection in lupus erythematosus) can provide an agent for an allergic injury to the skin which "sets off" the disastrous train of explosive reactions that destroys the patient with acute disseminate lupus erythematosus.

Treatment Conceptions and the Foregoing Theorization. It must be confessed that the contribution of a concept of infection-allergy to the treatment of lupus erythematosus is largely negative. It warns (1) that most lupus erythematosus is likely to become a grave problem if recognized too late—after the allergic changes in the vascular bed have become established in vital structures and grave damage is done. (2) It warns that disseminate cases are dynamite—must not be tested for tuberculosis with tuberculin, must not have infected teeth rashly extracted, or in periods of exacerbation. (3) It warns that sulfonamides must be used with the utmost caution, though helpful in some cases.[2,6,9,15,30,35,36,37,49,63,65,80,88,92,93] (4) The appearance of multiform erythematous as distinguished from discoid (follicular) lesions is of grave prognostic significance as suggesting involvement of the vascular bed, and a circulating "toxin" or allergen. (5) Leukopenia is an unfavorable sign, and thrombocytopenia even more so. (6) Fever, serous exudation, pulmonary symptoms and lymphatic enlargement, and especially albuminuria and impaired renal function are suggestive of the disseminate type and the existence of a deep as distinguished from a superficial process and injury.

The Early Diagnosis of Vasculo-Allergic and Disseminative Tendencies. How shall lupus erythematosus be recognized, suspected, or forestalled before it is clearly lupus erythematosus? (1) The preponderance of women, in the ages from puberty to menopause; (2) a history of light sensitiveness; (3) pallor and asthenic habitus with "fever of unexplained origin" (which is one of the synonyms for acute disseminate lupus erythematosus); (4) leukopenia, persistent and unexplained, especially during febrile episodes; (5) puffiness and persistent lividity of the lower eyelids; (6) thinning hair with no apparent local cause; (7) arthritoid manifestations in which the pain but not the fever responds to salicylates; (8) petechial eruptions; (9) slight albuminuria; (10) pleural, pericardial and endocardial signs with persistently negative blood cultures; these are, in various combinations, of considerable significance and the Reifensteins[69] and Rose and Pillsbury[70] even express willingness to make a diagnosis on these signs before the development of characteristic lesions.

Treatment. When once the process can be recognized, what can be done? It is not intended here to go into the therapy of the localized

discoid type. Gold therapy has not proved to be the radical cure that was hoped for, notwithstanding its good effect on many cases. Callaway and Stokes[13] pointed out the frequency of relapse and some of the factors influencing it. The now clearly recognized toxicity of gold is especially serious in cases threatening dissemination and there are no established benefits from its use in such cases.[1,7a,13,20,60,83,91,94] Bismuth is rated by Smith[79] and others[1,58,62,75,76,84,89] as equal in effectiveness to gold and materially safer, an experience with which the Reviewers agree. The non-specific quality of the effect is evident from the fact that neosilver arsphenamine for example, other trivalent arsenicals and even pentavalent arsenicals are also effective in some cases in which bismuth fails.[1,19,52,68,87] Other non-specific measures—liver extract, chaulmoogra oil—have been tried.[12,17,43,50,66,67]

In all types of erythematous lupus, the beneficial effect of *rest* can be observed; but it becomes paramount in those presenting threatening acute or disseminative manifestations. Rost gives it preëminence[72] in his discussion before the Strasbourg Reunion. The adjunct of *quinine* internally[18] is as much tradition as anything, but is supported by a number of experienced observers It should be pushed to at least 30 gr. a day. Its local use is mainly as a light-protective. *Protection from light* must be carried to the point in acute cases of keeping the patient in total darkness for days and weeks in order to tide over an acute light-exacerbative tendency. Nicotinic acid amide (nicotinamide) has also been used presumably with beneficial effects because of actions of light rays.[27,46] In the febrile agranulocytic and thrombocytic crises of the acute disseminate type, repeated small transfusions are as useful as anything. They may tide the patient over to a period of improvement, but the story of the ultimate outcome is told by figures such as those of the Mayo Clinic Group.[56]

The association of the acute disseminate type of erythematous lupus with the years of active menstrual function in women has led to assumptions of endocrine influence on the process. As a summary of the present extremely limited knowledge of the subject we are privileged to quote *in toto* a personal communication from Dr. Edward Rose who has been especially interested in this problem.

"The striking frequency with which the systemic exacerbations of acute disseminated lupus erythematosus exhibit a predilection for women in the active sexual phase of life (*i. e.*, between puberty and the menopause) has led to considerable speculation regarding the possible rôle of ovarian hormones in the disease. To date, no evidence has been presented which offers proof of any such relationship, but several attempts have been made to treat exacerbated lupus erythematosus in the female by suppressing ovarian function. Contratto and Levine[16] in 1939 reported the use of irradiation therapy to the ovaries in 1 case. Sossman and his associates* have employed this type of treatment in several other cases at the Peter Bent Brigham Hospital in Boston. Cluxton and Krause[14] mentioned irradiation of the ovaries as worthy of trial, in their review of acute disseminated lupus. Rose and Pillsbury† have collected 28 cases of acute disseminated lupus with systemic manifestations among whom 21 were females; 19 of these were in active menstrual life and 17 were between the ages of 14 and 30. In 1 of their male patients, the urinary excretion of 17-keto-steroids was low and the urinary excretion of pituitary follicle-

* Sossman, M., in personal communication to Dr. Edward Rose.
† Rose, E., and Pillsbury, D. M., unpublished data.

stimulating hormone was increased, suggesting hypogonadism with an increased estrogen-androgen ratio. Rose and Pillsbury* have observed the effects of inhibited ovarian function in 6 women with lupus erythematosus. Two of their patients showed only cutaneous lesions of the face. One of these women gave a history of premenstrual exacerbations of the skin lesions and showed marked improvement after a menopausal dose of Roentgen ray was given. The other patient has shown no marked improvement 10 months after irradiation menopause. One patient with a history of several acute systemic exacerbations has shown marked improvement since entering a natural menopause, while 1 patient whose clinical picture was complicated by probable bilateral apical pulmonary tuberculosis has remained well for 20 months after surgical castration (chronically infected Fallopian tubes were found and removed at the time of oöphorectomy). One patient died of renal failure several months after Roentgen ray castration, the clinical course of her disease apparently being unaffected by the procedure. One patient had had lesions limited to the face with premenstrual exacerbations for several years prior to a severe systemic exacerbation. Following irradiation menopause, the acute visceral phenomena subsided, leaving the patient with evidence of rather widespread vascular damage including extensive degeneration of the retinal vessels. This patient died 3 months after irradiation was given. These data quite obviously do not prove that castration in the female, whether accomplished surgically or by irradiation, is a therapeutic agent of value in the treatment of acute disseminated lupus erythematosus. However, in view of the extremely grave prognosis of the acute exacerbated form of this disease, it would appear justifiable to undertake further study of possible relationships between gonadal hormones and lupus erythematosus and to investigate the possible usefulness of castration in female patients more extensively."

By what mechanism the ovarian pituitary hormonal complex may be conceived to influence the infection-allergic picture of lupus erythematosus must be a matter of speculation. It is known that testosterone and hence possibly other endocrines of the gonadal system, congest the sebaceous gland and influence the behavior of the hair follicle.[33] Menstruation may be viewed, endocrinologically perhaps, as a repeated insult, against which the body immunizes itself. At least it may be associated with menotoxins or menotoxic manifestations of which Urbach[85b] has provided the most recent dermatologic, and Macht and his co-workers[53] the most massive general summary. Flares of infective processes on the skin (acne, staphylodermias) are known to occur in the premenstrual hydration period associated with the circulation of progesterone in the blood.[82] The relation of hydration to skin infection, especially pyogenic, has been discussed by the Reviewers elsewhere.[82] While it is not proposed to carry over what is known for the skin to other body tissues or infection in other structures, or to the allergic state at large, it is conceivable that recurring hydration and menotoxism so to speak, can underlie the gradual development of the infection hypersusceptibility and excessive reactivity of the victim of lupus erythematosus. Further reports on so radical a procedure as castration (induced menopause) in women in the child-bearing years will probably accumulate slowly but will be watched with interest.

* Data presented before national meeting of American Coll. Phys., Nov. 19, 1943, to be published.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF FEBRUARY 15, 1944

Protein-bound Iodine in Erythrocytes and Plasma and Elsewhere. By J. F. McClendon and Wm. C. Foster (Department of Physiology, Hahnemann Medical College). In 1938 we observed that precipitation of blood proteins with cold methanol and washing the precipitate with cold acetone completely removed added inorganic iodide but retained all the iodine of added thyroglobulin. In 1941 we showed that tissues powdered in liquid nitrogen gave similar values of protein-bound iodine. How could the thyroglobulin penetrate cells? We dissolved low iodine thyroglobulin from a goiter in bicarbonate-Ringer and stirred it with iodine crystals at 38° for 20 hours. The thyroxine and total iodine content had greatly increased. Perhaps proteins are iodinated inside tissue cells. (The effect of this thyroglobulin on the basal metabolic rate of rats had also increased.) Our method gives similar results to that of dialysis or precipitation of protein with zinc hydroxide. The following table indicates that the determination of protein-bound iodine in plasma has no advantages over its determination in whole blood as the corpuscles contain about as high a concentration as the plasma.

Protein-bound Iodine in Micrograms per 100 Cc.

Animal dialyzer	*Plasma*	*Erythrocytes*
Dog A,	5.4	4.5
$ZnSO_4$-NaOH	5.4	5.6
MeOH-acetone*	4.2	5.0
Dog B, "	4.5	5.5
Man A, "	4.2	5.2
Man B, "	5.0	4.9
Cow, "	6.8	6.4
Horse, "	9.2	7.4
Rabbit, "	11.1	11.2
Cat serum, "	7.6	7.2
Average	6.34	6.19

* CH_3OH-acetone.

Electrical Potential of Human Skin Measured on the Fingers. By T. CUNLIFFE BARNES (Department of Physiology, Hahnemann Medical College). Finger-tips were placed in cups of saline connected by salt bridges to silver chloride electrodes leading to a Micromax recording potentiometer. Fifty right-handed males had an average potential of 0.84 mv. positive on the right fingers measured against the homologous fingers of the left hand; 37 of these subjects were predominantly positive on the right side. Twenty left-handed males had an average finger potential of 0.13 mv. positive on the right; 6 of these subjects were predominantly positive on the left and 5 were isoelectric. These results support the data of Snodgrass (50 right-handed females with average of 1.7 positive on right and 4 left-handed females positive on the left).

Warming the skin made the potential more positive, augmented when the circulation was arrested by a cuff. At room temperature blocking the circulation usually produced negativity (the skin temperature fell to 28° C. or lower).

Muscular contraction (with or without circulation) made the finger potential positive (5 to 15 mv.) due to pressure on the cup serving as electrode. Clamping the relaxed finger gave the same effect. Pressure makes contact with the positive inner surface of the skin (Barnes, *Proc. Fed. Am. Soc. Exper. Biol.*, **1**, 6, 1942). Ethyl chloride, Sanborn electrode paste, camphor, chloroform and aluminum chloride made the skin negative (2 to 18 mv.). Mustard plaster raised the skin temperature 2° C. and produced 5 mv. positive.

Confirming Burr and also Melchoir (*Zentralbl. f. Chir.*, **45**, 598, 1918), skin wounds were positive (20 to 40 mv.). This positivity arises from the inner surface of the uninjured skin at the reference electrode (demonstrated by the change of potential produced by warming the skin).

In the frog cutting off the foot made the stump 20 mv. positive to the intact opposite leg. In man, allantoin, urea and sulfanilamide powder delayed healing (which was accelerated by yeast extract).

Alloxan Diabetes. By W. B. KENNEDY and F. D. W. LUKENS (Cox Institute, Univ. of Penna.). Diabetes was produced by the intravenous administration of alloxan in doses of 200 mg. per kg. of body weight, according to the method of Dunn, Sheehan and McLetchie (*Lancet*, **1**, 384, 1943). Ten rabbits which survived exhibited diabetes of moderate severity, with blood sugars which ranged from 300 to 700 mg. per 100 ml. Urinary excretion of glucose varied between 15 and 70% of the calculated available glucose in the diet. Nitrogen excretion in the fasting diabetic rabbit was not significantly increased over that in the normal rabbit. The islands of Langerhans showed early widespread necrosis which progressed to atrophy. Renal lesions, observed by others, were not found although in 2 rabbits an elevation of the blood urea nitrogen was found at death.

Excretion of Certain Newer Sulfonamides in the Bile and Urine. By HARRY SHAY, S. A. KOMAROV, H. SIPLET and S. S. FELS (Medical Research Laboratory, Samuel S. Fels Fund, Philadelphia). This study deals with the elimination of a few of the recently developed sulfonamides—especially phthalyl-sulfathiazole—with the bile and their fate in the gall bladder.

In addition, sulfathiazole, succinylsulfathiazole (sulfasuxidine), and sulfanilylguanidine (sulfaguanidine) were also studied.

Thirty acute experiments were carried out in fasting dogs under sodium pentobarbital anesthesia. Gall bladder and common bile duct were cannulated; a ligature was so placed on the common duct as to permit an independent flow of bile from a part of the liver to the gall bladder and from another part to the common duct distal to the point of ligation. The drugs were instilled in suspension in saline through the duodenal cannula in a dosage of 0.2 gm./k. Hepatic bile and urine were collected continuously and fractionated into 2-hour samples, while peripheral blood was taken at the end of each 2-hour period and the gall bladder was emptied at the same time. Such periods of observation lasted for 8 to 10 hours after the duodenal instillation of the drug.

Since the available preparations of sulfasuxidine and sulfathalidine both contained small amounts of free sulfathiazole as contaminants, we had both the free and conjugated forms of the drug to deal with when these compounds were studied. Marshall and his associates and Carryer and Ivy have shown that sulfanilamide is not acetylated by the dog's liver; we found the same to be true for sulfathiazole and sulfaguanidine.

All results after the 2-hour sample were averaged and averages are used in this report. The blood levels reached for sulfasuxidine and sulfathalidine were very low compared with sulfathiazole and even when compared with sulfaguanidine.

	Average blood level (mg. per 100 cc.)
Sulfathiazole	3.25
Sulfasuxidine	0.34
Sulfathalidine	0.19
Sulfaguanidine	1.12

Free sulfathiazole was concentrated in hepatic bile 2.3 times that of the blood level. While the "free form"—presumably also sulfathiazole—was concentrated in the bile after sulfasuxidine 2.4 times, after sulfathalidine, it was concentrated 11.4 times. These results appeared to indicate that sulfasuxidine was not broken down by the liver cell or bile while sulfathalidine was broken down to some extent. The liver appeared to excrete sulfaguanidine as a filtrate from the blood. The average blood and hepatic bile levels were identical at 1.12 mg. per 100 cc.

Sulfasuxidine concentration (5.29 mg. per 100 cc.) in hepatic bile was of somewhat lower magnitude than that found for sulfathiazole (7.48 mg. per 100 cc.). The bile/blood ratios, however, because of the much lower blood concentrations of sulfasuxidine were considerably greater for sulfasuxidine (38.3) than for sulfathiazole (2.3). In the case of sulfathalidine this difference was even more exaggerated. Average sulfathalidine in hepatic bile was 38.8 mg. per 100 cc. and the average bile/blood ratio was 206. The introduction of phthalic acid into the molecule greatly increased the elimination of the drug by the liver over that resulting from the introduction of succinic acid.

The gall bladder with all the drugs used except sulfaguanidine concentrated the drug brought to it with the hepatic bile in proportion to the water absorbed. This was established by finding that bile pigment and the drugs were concentrated in parallel by the gall bladder. There was no evidence of either absorption or excretion of the drugs by the gall bladder. With sulfaguanidine, there appeared to be some absorption of

the drug by the gall bladder since the gall bladder bile/hepatic bile ratio for the drug in 2 dogs were 2.5 and 1.5 as compared with their respective ratios for bile pigment of 4.3 and 3.1.

In the urine, sulfathiazole and sulfaguanidine appeared to be excreted by the glomerular filtration mechanism. There is accumulating evidence that sulfathiazole is handled by the kidney in such a manner. However, the concentration ratios (U/P) for sulfasuxidine and sulfathalidine reached such high levels that we suspect that these compounds are excreted by the tubules as well as by the glomeruli. However, a final conclusion must await the results of simultaneous creatinine and drug clearance studies which are now under way in our laboratory.

BOOK REVIEWS AND NOTICES

MEDICAL RADIOGRAPHIC TECHNIC. Edited by GLENN W. FILES, Director of General Electric *X*-Ray Corporation Technical Service Department. Pp. 365; 381 figs. Springfield: Charles C Thomas, 1943. Price, $6.00.

THE contents of this book are largely divided into 3 categories: (1) Fundamental electrical concepts concerning the various units of the Roentgen ray equipment; (2) Processing; (3) Radiographic technique, with an excellent chapter on osteology as it concerns the radiographic technician.

The positions illustrated are the routine positions utilized largely by the Technical Service Department of the General Electric Corporation. The portrayals are magnificent and they have utilized diagrams and photography and Roentgen illustrations to good advantage.

This book on medical technique is in no way complete, however, and it is most unfortunate that Mr. Files has not utilized many methods that are conventional in general Roentgen ray departments. For instance, it has been recognized for years that the examination of the paranasal sinuses and of the head should be made in the erect posture. All of the illustrations given are in the horizontal posture. This, of course, means that if the book is widely used, many radiographic technicians will automatically plan their examinations in the horizontal posture, with the result that diagnoses, readily made from films of the erect posture, will become more difficult or be missed entirely.

The Reviewer does not mean to condemn this book by the above comments; he would recommend that it be in the hands of every radiographic technician and in the radiographic rooms of all Roentgen ray departments. It is to be hoped, however, that in the second edition of this book, that the authors will seek the help of some of their medical friends concerning additional radiographic technique that might, with propriety and extreme usefulness, be included in such a volume.

The publisher has maintained his usual standard in this book. The figures with two colors, the photographic illustrations and the illustrations of roentgenograms are magnificent. The paper is excellent and the print is easy to read.

E. P.

A HUNDRED YEARS OF MEDICINE. By C. D. HAAGENSEN and WYNDHAM E. B. LLOYD. Pp. 444. New York: Sheridan House, 1943. Price, $3.75.

WYNDHAM LLOYD'S "A Hundred Years of Medicine" was published as a book of 344 pages in 1936. Now, C. D. Haagensen, a surgeon-pathologist at Columbia who has long been concerned with medical history—has substantially revised all but the first fourth of the work and added chapters on the more recent paths of progress, such as chemotherapy, vitamins, thoracic surgery, and a new Part IV on New Social Aspects of Medicine. In Part I, "Medicine up to a Hundred Years Ago" (55 pages), brief high lights are given chiefly of the 18th century, on such topics as origins and theories of disease, scientific progress, surgery, hospitals, infectious diseases, the medical profession.

Medical Science of the past century (Part II) and Surgery for the same period (Part III) make up the bulk of the book. Even educated physicians will be surprised to realize how much of the story of medicine falls into this period—the new pathology, the germ theory, aids to diagnosis, chemotherapy, tuberculosis, vitamins, pernicious anemia, diabetes, cardiovascular disease,

nephritis. Such are the subjects picked to illustrate the century of medical progress, with an equivalent list for surgery. Virchow, Pasteur, Koch, Folin, Ehrlich, Domagk, Laennec (incidentally he no longer falls within the century limit), Trudeau, Banting, Mackenzie are the medical leaders portrayed both in illustration and text, with McDowell, Morton, Lister, Halsted, Semmelweis, Hugh Thomas, Harvey Cushing, in Surgery.

In the new Part IV, New Social Aspects of Medicine, Dr. Haagensen, after a brief summary of the progress made in advancing public health, departs from the rôle of historian to give an interesting, simple yet adequate presentation of the doctor's dilemma—how best to use our great mass of medical knowledge for the benefit of society, in order to bring the best, even though expensive, medical care within the grasp of all the people. Government support of hospitals, sickness insurance (governmental and voluntary), group practice, the Baker Memorial, are presented in a non-committal way that is especially timely now when the Wagner-Murray Bill threatens this country.

Thus, in phraseology too simple to repel even the simplest reader, is presented the progress of medicine during a period when it has advanced most rapidly in all its history—a leading science in an age of science and the one that affects individuals most acutely. The story is accurately told, with perhaps too much emphasis here and there on the author's favorites. The text is entertainingly presented, more so than in the earlier edition, and spiced with a good proportion of personal details. A defect easily remedied in later editions is that the illustrations appear entirely outside of the text that they are intended to illustrate: thus, Laennec's portrait faces the discovery of insulin; Banting's portrait and The Coming of Anesthesia make strange bedfellows; while the Curies keep surprising company with problems of specialization in medical practice. However, this is indeed a minor defect in an otherwise excellent book.

E. K.

MEDICAL CLINICS OF NORTH AMERICA. Philadelphia Number (November 1943). Symposium on Medical Emergencies on the Home Front. Pp. 280. Philadelphia: W. B. Saunders Company, 1943. Price, $16.00 per year.

THIS number of the Medical Clinics maintains the proven worth of this series of monographs. The busy war-time practicing physician will appreciate this volume for it makes immediately available practical information which otherwise must be culled from a variety of sources at a cost of considerable time. One might not agree with individual points of view concerning certain specific therapies, but in general each author has done a commendable and practical job.

Among the original contributions offered in this issue, the article on Sulfamerizine by Dr. Flippin and associates is worthy of note, for it seems evident that this new sulfonamide drug will occupy an important place in prophylaxis and therapy.

F. M.

ELECTRONIC INTERPRETATIONS OF ORGANIC CHEMISTRY. By A. EDWARD REMICH, PH.D., Assistant Professor of Chemistry, Wayne University, Detroit. Pp. 474. New York: John Wiley & Sons, Inc., 1943. Price, $4.50.

THIS book will contribute to the armamentarium of those organic chemists who, for obvious reasons, are dependent upon empirical knowledge and intuitive reasoning for the successful prosecution of their research. Those who are unfamiliar with modern electronic theory and the numerous applications of modern physical chemistry to organic chemistry will find this book invaluable as an introduction to the field. To avoid misunderstanding, the Reviewer hastens to add that the subject matter is extensively reviewed and discussed in a critical manner.

The first 3 chapters are devoted to a historical consideration of valence and

chemical affinity, ending with applications of the Lewis theory to problems of molecular structure. The development by the English school and the foundation upon which it rests are reviewed critically and presented in logical fashion in the following 2 chapters. There is an extensive discussion of the many applications of these theories to organic reactions and behavior. The remaining chapters are devoted to a critical discussion of the manner in which modern physics and physical chemistry have supported and extended these applications. An imposing number of organic reactions are critically discussed from this point of view. The appendix contains elementary presentations of the Lewis theory, refractively, dipole moments, reactions in non-aqueous solutions, and modern theories of acid-base relationships.

The author has attempted to organize those concepts which are sound into a set of working rules for the organic chemist; he speaks the language of the organic chemist as much as it is possible for one to do so. Although there is undoubtedly much debatable ground and the ever-present danger of oversimplification, nevertheless the end justifies the means. To the advanced student as well as to many organic chemists, this book will open new horizons.

S. G.

THE BRITISH ENCYCLOPÆDIA OF MEDICAL PRACTICE, including Medicine, Surgery, Obstetrics, Gynecology, and Other Special Subjects. MEDICAL PROGRESS, 1943 (Pp. 382); CUMULATIVE SUPPLEMENT, 1943 (Pp. 342; 5 figs.). Under the General Editorship of SIR HUMPHRY ROLLESTON, BART., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Sometime President of the Royal College of Physicians of London. London, Eng., and Toronto, Can.: Butterworth & Co. (Publishers), Ltd., 1943.

ACCORDING to their customary procedure, the publishers have issued their 1943 cloth-bound volume of Medical Progress, together with the Cumulative Supplement, which is bound in stout cardboard.

In the Medical Progress volume—the 4th annual supplement—Part 1 presents 16 signed critical surveys of timely subjects; Part 2, a single article on Recent Developments in Drug Therapy; and Part 3—the larger part of the book—a few hundred brief summaries, arranged alphabetically. For instance, Herpes (based on 2 articles), Histoplasmosis (based on 2 articles) and Hodgkin's Disease (based on 7 articles) together require 2¼ pages.

The Cumulative Supplement aims to contain "fresh knowledge of a type likely to remain established." Its system of Key Numbers, at the top right-hand corner of each page, facilitates use in connection with the original volumes, which are key-numbered in the same way. As to the examples selected above, Herpes and Histoplasmosis are covered by 2 lines each of cross-references, whereas Hodgkin's Disease receives 3 pages.

Though such books are practically impossible to evaluate and report upon in writing, it appears to the Reviewer that literary British medicine continues to "pull its weight" remarkably well in spite of the grievous handicaps of war conditions.

E. K.

UROLOGY FOR NURSES. By OSWALD SWINNEY LOWSLEY, M.D., F.A.C.S., Director of the Department of Urology (James Buchanan Brady Foundation) of the New York Hospital, and THOMAS JOSEPH KIRWIN, M.D., F.A.C.S., Attending Urologist of the Department of Urology (James Buchanan Brady Foundation) of the New York Hospital. New Printing. Pp. 493; 108 illus. Philadelphia: J. B. Lippincott Company, 1943. Price, $3.00.

THE authors present a new printing of their already popular text on urologic nursing. Much new material, covering recent developments in urology, is given. Throughout the book the rôle of the nurse, as applied to the field of urology, is stressed. The precision necessary for good results in urology

requires that nurses taking care of such patients have special training in that field.

A short introductory chapter gives the historical background of the development of urology as a special field in medicine. This is followed by a chapter on the psychic and social aspects peculiar to the field of urology.

Laboratory tests and technical procedures used in diagnosis are presented in such a manner that the rôle of the nurse is emphasized. The many instruments used in urologic study are described and their care discussed.

Beginning with the sixth chapter, the organs of the urinary and genital tracts are considered in their anatomic sequence from within outward, beginning with the kidneys and concluding with the external genitalia. The embryologic, anatomic and physiologic aspects of each organ are considered. These discussions are followed by information on the diseases of each organ. Again the nurse's part in the care of such diseases is stressed.

A summary of recent urologic developments appearing since the first printing of this book in 1936 is given. Such information includes points concerning diagnosis, treatment, diets and technical procedures.

It is fortunate that such a reference and text-book exists. The urologist knows so well the importance of an intelligent and well-informed nurse in the care of patients with urologic disease. Nurses, medical students and physicians interested in the care of urologic patients would do well to read this excellent book.

L. LaT.

THE ARTHROPATHIES. A Handbook of Roentgen Diagnosis. By ALFRED A. DE LORIMIER, A.B., M.A., M.D., Colonel, Medical Corps, U. S. Army; Commandant, The Army School of Roentgenology, Memphis, Tenn. Formerly Director, Department of Roentgenology, Army Medical School, Washington, D. C. Pp. 319; 678 figs. Chicago: The Year Book Publishers, Inc., 1943. Price, $5.50.

THIS book, the first of a series, contains a wealth of material beyond what might be assumed from its title. By convention, the term "arthropahy" has not been generally applied to conditions like congenital rickets, scurvy, fractures and neoplasms. It is to be hoped, therefore, that the unusual though logical choice of title will not limit its sale or usefulness.

The author, a man of tremendous experience, has succeeded in presenting a wealth of material briefly and satisfactorily; but the usefulness of this book will be greatly limited by what the Reviewer believes is poor publishing. The paper is so poor that unless the light strikes the print just right, one cannot see it well. The illustrations, although the originals may have been good, lose a tremendous amount of their value because of the nature of the paper used for portraying the illustrations. The illustrations are well set on the page, but their descriptions are marred by the curved arrows, the difficulty in finding the description of a given illustration, and the very small print used in the legend. One gets almost "woozy" in trying to connect the legend with the proper illustration; and when it is found one discovers the value of the illustration has been ruined by multiple curved arrows.

The author has in a masterly fashion developed the importance of regarding the Roentgen examination as a consultation; and he has indicated in detail the various roentgenologic factors that should be considered in analyzing the joints and the items of clinical importance with which the Roentgen findings should be correlated.

The Reviewer believes that this handbook is one of the best that has been prepared on this particular subject, and it is most unfortunate that the publisher did not use better paper and better print. It is to be hoped that in the succeeding handbooks this phase will be corrected. Page 129 is a good example of a place where larger print could have been used with ease without sacrificing anything. Likewise, on pages 72, 73, 77 and 116 one can see where too many curved arrows have been utilized.

In spite of the above criticism, I believe that this book is eminently worthwhile and should prove of value to anyone interested in this subject.

E. P.

A CATALOGUE OF THE MEDIEVAL AND RENAISSANCE MANUSCRIPTS AND INCUNABULA IN THE BOSTON MEDICAL LIBRARY. Compiled by JAMES F. BALLARD, Director, Boston Medical Library. Pp. 246; 23 figs. Boston: Privately Printed.

IN the number and importance of its Medical Manuscripts and Incunabula, the Boston Medical Library has been *facile princeps* in this country since the acquisition of the Bullard Collection (179 incunabula) in 1931. With 52 ancient manuscripts (written before 1501?) and 674 Incunabula, well distributed over the field of 15th century medical literature, this collection still stands well ahead of those in the Surgeon-General's Library, The College of Physicians of Philadelphia and the New York Academy of Medicine. In fact, when one considers that in Klebs' *Incunabula Scientifica et Medica*, of the 3000 editions given, only 850 are listed as medical, and, further, that many of the rarer items in public institutions are permanently off the market, one realizes what a rich treasure awaits students in the field in Boston. Future acquisitions should be few and far between. All this, coupled with Mr. Ballard's, the Compiler's, recent completion of 50 years of service to The Boston Medical Library, constitutes more than ample *raison d'être* for the publication of this handsome "Catalogue."

The collection apparently will continue to follow Dr. Bullard's aim of reproducing, as far as possible, a learned 15th century physician's library. This, incidentally, gives the Introducer, Dr. Henry Viets, an opportunity to consider, in a few pleasant pages, "our knowledge of what such a hypothetical library might contain." One wishes that this section might have been further expanded.

The book is welcome, not only for its content, but for its highly creditable editing and publishing. The Preface and Introduction are informative, clear and entertaining. The method of presentation is good. A number for each item, both in the lists and the textual references, is very convenient, as are the concordances and the name index. The occasional annotations are helpful and the illustrations adequate. The Compiler's competence in this field is a far better guarantee of the scholarly accuracy of the text than any recommendation that the Reviewer could make. E. K.

NEW BOOKS

Textbook of Anatomy and Physiology. By CATHERINE PARKER ANTHONY, B.A., R.N., Instructor of Anatomy and Physiology, Lutheran Hospital, Cleveland, Ohio; Formerly Instructor of Anatomy and Physiology, Frances Payne Bolton School of Nursing, Western Reserve Univ. Pp. 400; 33 tables; 153 illus. (8 color plates). St. Louis: C. V. Mosby, 1944. Price, $3.50.

Oral Histology and Embryology. Edited by BALINT ORBAN, Foundation for Dental Research of the Chicago Coll. of Dental Surgery, School of Dentistry, Loyola Univ. Pp. 342; 9 tables; 262 illus. (4 color plates). St. Louis: C. V. Mosby, 1944. Price, $6.50.

Strophanthin. Clinical and Experimental Experiences of the Past 25 Years. By BRUNO KISCH, M.D., Formerly: Professor on the Medical Faculty of Cologne Univ. (Germany), Visiting Professor to the International Univ. in Santander (Spain), Research Fellow at Yale Univ. Pp. 158; 24 figs; 11 tables. New York: Brooklyn Medical Press, 1944. Price, $4.00.

What is Hypnosis. Studies in Conditioning. By ANDREW SALTER. Pp. 88. New York: Richard R. Smith, 1944. Price, $2.00.

Medical Physics. Editor-in-Chief, OTTO GLASSER, PH.D., Head, Department of Biophysics, Cleveland Clinic Foundation; Professor of Biophysics, Frank E. Bunts Educational Institute; Consulting Biophysicist, University Hospitals of Cleveland, Cleveland, Ohio. Pp. 1744; many figs and tables. Chicago: Year Book Publishers, 1944. Price, $18.00.

Civilization and Disease. By HENRY E. SIGERIST, M.D., D.LITT., LL.D., William H. Welch Professor of the History of Medicine in the Johns Hopkins Univ. Pp. 255; 52 figs. Ithaca, N. Y.: Cornell Univ. Press, 1943. Price, $3.75.

Clinical Tropical Medicine. By Twenty-seven Authors. Edited by Z. TAYLOR BERCOVITZ, M.D., PH.D., F.A.C.P., Assistant Clinical Professor, New York Post-Graduate Med. School, Columbia Univ.; Physician-in-Charge, Parasitology Service, Department of Health, City of New York; Consultant in Tropical Medicine, Ellis Island Hospital, United States Public Health Service. Foreword by WILBUR A. SAWYER, M.D., Director, International Health Division, Rockefeller Foundation. Pp. 957; 121 figs; 11 tables. New York, London: Paul B. Hoeber, 1944. Price, $14.00.

Physical Foundations of Radiology. By OTTO GLASSER, PH.D., Professor of Biophysics and Head of Department of Biophysics, Cleveland Clinic Foundation, Cleveland, Ohio; EDITH H. QUIMBY, Sc.D., Associate Professor of Radiology (Physics), Coll. of Physicians and Surgeons, Columbia Univ., New York; LAURISTON S. TAYLOR, PH.D., Chief of *X*-ray Section, National Bureau of Standards, Washington, D. C.; and J. L. WEATHERWAX, M.A., Philadelphia General Hospital and Graduate School of Medicine, Univ. of Penn., Philadelphia. Pp. 426; 95 figs; 43 tables. New York and London: Paul B. Hoeber, 1944. Price, $5.00.

The 1943 Year Book of Pediatrics. Edited by ISAAC A. ABT, D.Sc., M.D., Professor of Pediatrics, Northwestern Univ. Med. School; Attending Physician, Passavant Hospital; Consulting Physician, Children's Memorial Hospital and St. Luke's Hospital, Chicago. With the Collaboration of ARTHUR F. ABT, B.S., M.D., Associate Professor of Pediatrics, Northwestern Univ. Med. School; Associate Attending Pediatrician, Michael Reese Hospital; Attending Pediatrician, Chicago Maternity Center; Attending Physician, Spaulding School for Crippled Children and La Rabida Jackson Park Sanatorium, Chicago. Pp. 448; 76 figs. Chicago: Year Book Publishers, 1944. Price, $3.00.

Old Age in New York City. By HELEN HARDY BRUNOT. Pp. 128; many tables. New York: Welfare Council of New York City, 1944. Price, $1.50.

Behind the Universe. A Doctor's Religion. By LOUIS BERMAN, M.D. Pp. 303. New York and London: Harper & Bros., 1943. Price, $2.75.

Medical Care of the Discharged Hospital Patient. By FRODE JENSEN, M.D., Instructor in Medicine, Syracuse University College of Medicine; H. G. WEISKOTTEN, M.D., Dean and Professor of Pathology, Syracuse University College of Medicine; and MARGARET A. THOMAS, M.A. (OXON.). Pp. 94; 4 tables. New York: Commonwealth Fund, 1944. Price, $1.00.

Maurice Arthus' Philosophy of Scientific Investigation. Preface to De l'Anaphylaxie a' l'Immunité, Paris, 1921. Translated from the French, with an Introduction by HENRY E. SIGERIST. Foreword by WARFIELD T. LONGCOPE. (Reprinted from Bulletin of the History of Medicine, **14**, No. 3, p. 366, October, 1943.) Pp. 26. Baltimore: Johns Hopkins Press, 1943. Price, $.75.

Authority in Medicine: Old and New. By MAJOR GREENWOOD, D.Sc., F.R.C.P., F.R.S., Professor of Epidemiology and Vital Statistics in the Univ. of London. The Linacre Lecture, May 6, 1943. Pp. 32. Cambridge: University Press; London: Bentley House; New York: Macmillan, 1943. Price, $.40.

The March of Medicine. New York Academy of Medicine Lectures to the Laity, 1943. Pp. 151. New York: Columbia Univ. Press, 1943. Price, $2.00.

The Hippocratic Oath. Text, Translation and Interpretation by LUDWIG EDELSTEIN. Supplements to the Bull. of Hist. of Med., Editor: Henry E. Sigerist, No. 1. Pp. 64. Baltimore: Johns Hopkins Press. Price, $1.25.

Occupational Lead Exposure and Lead Poisoning. Report of the Committee on Lead Poisoning of the Industrial Hygiene Section, A.P.H.A. Pp. 67. New York: American Public Health Assn. Price, $.75.

A useful guide to (1) practical and effective measures for the recognition and prevention of hazardous lead exposure in industry; (2) methods for the differential diagnosis and treatment of lead intoxication, and (3) the factual requirements for medico legal purposes. A 6-page classified bibliography will guide the reader to further study.

Baby Doctor. By ISAAC A. ABT, M.D. Pp. 308. New York and London: Whittlesey House, McGraw-Hill, 1944. Price, $2.50.

Medicine and the War. Edited by WILLIAM H. TALIAFERRO. Foreword by WILLIAM T. HUTCHINSON, Executive Secretary, Charles R. Walgreen Foundation for the Study of American Institutions. Pp. 193; several figs. and tables. Chicago: Univ. of Chicago Press. Price, $2.00.

The Religious and Philosophical Aspects of van Helmont's Science and Medicine. By WALTER PAGEL. Supplements to the Bull. of Hist. of Med., Editor: Henry E. Sigerist, No. 2. Pp. 44. Baltimore: Johns Hopkins Press. Price, $1.00.

Evolucion y Funcion Biologica de las Proteinas. (Six lectures given in the Amphitheater of the School on May 4, 7, 11, 13, 18 and 20, 1943.) By JULIO MENDEZ, Physician of the J. M. Ramos Mejia Hospital. Pp. 139; 4 charts. Buenos Aires: Guillermo Kraft, 1943.

Primer Congreso Nacional Sobre Enfermedades Endemo-epidemicas. (From First National Congress on Endemo-epidemic Diseases, held at the "Instituto Jose Penna," School of Medical Sciences of Buenos Aires, November, 1942. Pp. 679; many tables and figs. Buenos Aires: Revista Oral de Ciencias Medicas, 1943.

Safe Convoy. The Expectant Mother's Handbook. By WILLIAM J. CARRINGTON, M.D., A.B., F.A.C.S., Attending Gynecologist, Atlantic City Hospital, Atlantic County Hospital for Nervous and Mental Diseases, Pine Rest Hospital, Atlantic City Municipal Hospital and Atlantic Shores Hospital; Diplomate, American Board of Obstetrics and Gynecology; Former Vice-President, American Medical Association. Pp. 253. Philadelphia, New York: J. B. Lippincott, 1944. Price, $2.50.

NEW EDITIONS

Pioneers of Pediatrics. By ABRAHAM LEVINSON, M.D., B.S., Assistant Professor of Pediatrics, Northwestern Univ. Med. School; Professor of Pediatrics, Cook County Graduate School of Medicine; Attending Pediatrician, Children's Division of the Cook County Hospital; Senior Attending Pediatrician, Sarah Morris Hospital for Children of the Michael Reese Hospital; Senior Attending Pediatrician, Mount Sinai Hospital, Chicago. Foreword by ISAAC A. ABT. Second ed., revised and reset. 15th Publication in *Historia Medicinae* Series. Pp. 118; many pictures. New York: Froben Press, 1943. Price, $2.00.

The Care and Feeding of Children. By L. EMMET HOLT, M.D., revised and enlarged by L. EMMET HOLT, JR., M.D., Associate Professor of Pediatrics, Johns Hopkins Univ.; Associate Pediatrician, Johns Hopkins Hospital, Baltimore, Md. Sixteenth ed., revised and enlarged. Pp. 321; a few figs. New York and London: D. Appleton-Century. Price, $2.00.

Manometric Methods as Applied to the Measurement of Cell Respiration and Other Processes. By MALCOLM DIXON, PH.D., SC.D., F.R.S., University Lecturer in Biochemistry in the Univ. of Cambridge. Foreword by SIR F. G. HOPKINS, O.M., F.R.S. Second ed. Pp. 155; 20 figs.; 6 tables. Cambridge: University Press; New York: Macmillan. Price, $1.75.

Synopsis of Obstetrics. By JENNINGS C. LITZENBERG, B.SC., M.D., F.A.C.S., Professor Emeritus of Obstetrics and Gynecology, Univ. of Minn. Med. School, Minneapolis, Minn. Second ed. Pp. 405; 157 illus. (5 in color). St. Louis: C. V. Mosby, 1943. Price, $5.00.

Synopsis of Materia Medica, Toxicology, and Pharmacology. For Students and Practitioners of Medicine. By FORREST RAMON DAVISON, B.A., M.Sc., PH.D., M.B., Formerly Assistant Professor of Pharmacology in the School of Medicine, Univ. of Arkansas, Little Rock Ark.; Medical Department, The Upjohn Co., Kalamazoo, Mich. Third ed. Pp. 759; 40 illus. (4 in color); 35 tables. St. Louis: C. V. Mosby, 1944. Price, $6.50.

Oral Pathology. A Histological, Roentgenological, and Clinical Study of the Diseases of the Teeth, Jaws, and Mouth. By KURT H. THOMA, D.M.D., Professor of Oral Surgery and Brackett Professor of Oral Pathology, Harvard Univ.; Oral Surgeon and Chief of Dental Service, Massachusetts General Hospital; Oral Surgeon to Brooks Hospital; Dental Surgeon to Dental Department and Consultant in Oral Surgery to Tumor Department, Boston Dispensary and Joseph H. Pratt Diagnostic Clinic; Consulting Oral Surgeon, New England Baptist Hospital; Consulting Oral Surgeon, Beth Israel Hospital. Second ed. Pp. 1328; 1388 figs. (128 in color); 49 tables. St. Louis: C. V. Mosby, 1944. Price, $15.00.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa. Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

MANUSCRIPTS should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. The recommendations of the American Medical Association Style Book should be followed. REFERENCES should be numbered and at the end of the articles, arranged alphabetically according to the name of the first author and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

NEW NOTICE TO CONTRIBUTORS AND SUBSCRIBERS

Activated by a directive from the War Production Board, we have changed the size of our type page for the "duration" to effect an economy in the amount of paper used. While there is a smaller number of pages, the amount of material has not been noticeably reduced.

We hope that any unpleasant effect produced by cutting down the margins will be accepted and approved by readers as a temporary war casualty. It is possible that more radical changes will have to be made later, but we are loath to change any more than absolutely necessary, a format that has existed practically unchanged since the Journal began in 1820.

For the balance of the war, 150 reprints will be supplied gratis. Covers will be omitted on all articles. In ordering additional reprints, we will supply in multiples of 150. This modification is for the same reason as the change of format, *i. e.*, conservation of paper.

NOTICE TO SUBSCRIBERS AND ADVERTISERS

We desire to secure several copies of the March and May 1943 numbers of this Journal, in order to comply with requests and need for replacements in long library "runs." The war situation has made it impossible to print extra numbers to supply this demand. We would be *very* grateful to anyone who would return to the Publishers any unmutilated copies of these numbers for which they have no further use, and we would be glad to repay postage.